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Screening for Depression, Anxiety, and Suicide Risk in Adults: A Systematic Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: To review the benefits and harms of screening and treatment for depression, anxiety, and suicide risk, and the accuracy of instruments to detect these conditions among primary care patients.

Data Sources: MEDLINE, PsychINFO, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews through September 9, 2022, bridging from prior USPSTF reviews or other relevant reviews. Eligible studies included in the prior reviews were also included. We conducted ongoing surveillance for relevant literature through November 25, 2022.

Study Selection: We reviewed 23,497 abstracts and assessed 1237 full-text articles against a priori inclusion criteria. We included English language studies of screening or treatment (compared to control conditions), or test accuracy of a priori selected screening instruments. Primary studies of screening and test accuracy were limited to primary care populations, as were primary studies of anxiety treatment. Primary studies of suicide prevention treatment that recruited from non-acute outpatient settings were included. Included study design varied by condition and key question; primary trials and test accuracy studies were used for smaller evidence bases, and existing systematic reviews (ESR) were used for large, mature bodies of literature. Observational studies and ESRs of observational studies were included for harms of pharmacotherapy. Critical appraisal was completed independently by two investigators for primary research. ESRs were appraised by a single reviewer and confirmed by a second reviewer if minimum quality standards were not met. Data were extracted from studies by one reviewer and checked by a second.

Data Analysis: Where primary research evidence was sufficient for pooling, we conducted random effects meta-analysis using the DerSimonian & Laird or restricted maximum likelihood method with the Knapp-Hartung correction for a small number of studies. Where possible, subgroup analysis and meta-regression were used to explore effect modification. Pooled results from ESRs were presented in tables and forest plots.

Results: 185 studies (86 ESRs and 99 primary studies) were included, covering an estimated 13 million persons, across all conditions and key questions. Depression screening interventions, many of which included additional intervention components, were associated with a lower prevalence of depression or clinically important depressive symptomatology after six to twelve months (OR, 0.60 [95% CI, 0.50 to 0.73]; 8 RCTs [n=10,244]; I^2=0%). Several instruments demonstrated adequate test accuracy (e.g., sensitivity 0.82 [95% CI, 0.76 to 0.86], specificity 0.87 [95 % CI, 0.84 to 0.89] for the patient health questionnaire (PHQ)-2 followed by the full PHQ-9 if the PHQ-2 is positive), and a large body of evidence supported benefits of psychological and pharmacologic treatment of depression. A pooled estimate from trials used for FDA approval data suggested a very small increase in the absolute risk of a suicide attempt with second generation antidepressants (OR, 1.53 [1.09 to 2.15]; N= 40,857; 0.7% of antidepressants users had a suicide attempt vs 0.3% of placebo users; median followup, 8 weeks). Two screening studies found no benefit for screening for anxiety. Among test accuracy studies, only the GAD-2 and GAD-7 were reported by more than one study and demonstrated adequate accuracy for

detecting generalized anxiety disorder (e.g., sensitivity 0.84 [95% CI, 0.74 to 0.94], specificity 0.87 [95 % CI, 0.80 to 0.93] for the GAD-7 at a cutoff of 9). Evidence was limited for other instruments and other anxiety disorders. A large body of both primary and ESR evidence supports the benefit of treatment for anxiety. One RCT (n=443) of a suicide risk screening intervention found no reduction in suicidal ideation after two weeks; three studies of suicide risk test accuracy were included with no replication of any instrument; and suicide prevention studies did not demonstrate an improvement over usual care, and one large (n=18,883) trial found an increased risk of suicide attempts associated with a low-intensity online intervention in addition to usual mental health care, compared with usual mental health care alone.

Limitations: Suicide prevention treatment studies typically used usual or optimized specialty mental health care as control groups, so could be considered comparative effectiveness. Limiting the examination of anxiety screening instruments to prespecified a priori instruments may have excluded some relevant studies. The use of ESRs may have limited our ability to examine effects in some specific patient populations.

Conclusions: Both direct and indirect evidence support depression screening in primary care settings, including during pregnancy and postpartum. While evidence is insufficient to draw conclusions about the benefits or harms of anxiety screening interventions, there is clear evidence that treatment for anxiety is beneficial, and more limited evidence indicating acceptable accuracy of some anxiety screening instruments to detect generalized anxiety disorder. There are numerous important gaps in the evidence for suicide risk screening in primary care settings.

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Chapter 1. Introduction

Purpose

The Agency for Healthcare Research and Quality (AHRQ) has requested a review on screening and treatment for depression, anxiety disorders, and suicide risk in adults, including pregnant people. This topic includes updating the evidence for two previous USPSTF reviews, Screening for Depression in Adults[1] and Screening for Suicide Risk in Primary Care,[2] and a new topic of screening for anxiety disorders. This report will be used by the U.S. Preventive Services Task Force (USPSTF) to update its 2016 recommendation for Screening for Depression in Adults and its 2013 Screening for Suicide Risk in Primary Care, and to develop a new recommendation on screening for anxiety disorders.

Condition Background

Condition Definitions

Depression

Major Depressive Disorder (MDD) is a mood disorder characterized by persistent feelings of sadness and loss of interest in usually pleasurable activities, and may be accompanied by irritability, changes in sleeping patterns and appetite, aches and pains, restlessness, and feelings of low self-worth.[3] The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) describes depression as a "common and serious medical illness that negatively affects how you feel, the way you think, and how you act."[4] Perinatal depression refers to major and minor depressive episodes that occur during pregnancy and the postpartum period, which is often defined as the first 12 months following delivery.[5] In addition to the typical symptoms of depressive disorders (e.g., feeling hopeless, loss of interest in activities that used to be enjoyed, withdrawing from friends and family), other symptoms in the perinatal period may also include a persistent doubt of the ability to take care of the infant, trouble bonding with or forming an emotional attachment with the infant, and thoughts of death, suicide, self-harm or harm of the infant.[6]

Anxiety

Anxiety disorders are characterized by excessive and persistent fear and anxiety about everyday events, along with related behavioral and somatic complaints such as autonomic arousal, restlessness, fatigue, problems concentrating, irritability, and sleep problems.[4] Anxiety disorders include generalized anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, specific phobias, separation anxiety disorder, selective mutism, substance/medication-induced anxiety disorder, anxiety disorder due to another medical condition, and anxiety not otherwise specified.

Suicide Risk

Suicide is defined as an intentional act of inflicting one's own death. Suicide attempts and ideation (thoughts of killing oneself or wishing to be dead), as well as self-harm (a broader term that includes suicide attempts as well as self-injury without intent of death) are more common than suicide deaths and often signal a precursor to suicide and a potential intervention point.[7] However, it can be challenging to ascertain the intent of patients with self-inflicted injury. Suicide, suicide attempts, suicidal ideation, and self-harm can occur with various psychiatric diagnoses, including depressive and anxiety disorders.[7]

Prevalence and Burden

Depression

Depression is a common mental disorder in the US, with substantial economic costs. In 2019, an estimated 7.8 percent of US adults (19.4 million adults) experienced at least one major depressive episode and 5.3 percent of adults (13.1 million individuals) experienced a major depressive episode with severe impairment (**Table 1**).[8] The average prevalence of postpartum depressive symptoms across 31 sites was 13.2 percent in 2018,[9] according to the Data from the Pregnancy Risk Assessment Monitoring System (PRAMS). Aggregate data from the PRAMS survey showed an increase in self-reported depression during pregnancy from 11.6 percent in 2016 to 14.8 percent in 2019.[10]A study using national survey and administrative claims data found that between 2010 and 2018, the incremental economic burden of individuals with MDD alone increased by 37.9% from $236.6 billion to $326.2 billion (2020 values).[11]

Women have nearly double the risk of depression compared to men, though the mechanisms underlying this disparity are unclear. It has been hypothesized that social and economic circumstances, as well as biology (e.g., endocrine or neurobiological differences, pregnancy and postpartum changes) may contribute to this gap.[12, 13] In addition to varying by sex, prevalence rates among the general American adult population vary by age, race and ethnicity, education, geographic location, poverty level, and employment. Young adults, multiracial, and Native American/Alaska Native individuals experience higher rates of depression.[14]

Depression has a significant impact on quality of life, personal relationships, and self -care.[15] Depression, especially untreated, is associated with increased mortality, higher risk of cardiovascular events, and may exacerbate comorbid conditions.[16-18] Depression during pregnancy increases the risk of preterm birth and small-for-gestational age[19, 20] infants, and postpartum depression interferes with optimal parenting to promote infant bonding.[21] A systematic review exploring neonatal risks associated with untreated prenatal depression found that pregnant women with untreated depression had an increased risk of both preterm birth and low birthweight compared with women without depression.[20] A Canadian study found that young children exposed to maternal depression had a 17 percent higher risk of having at least one developmental vulnerability at school entry, such as difficulties in social competence (adjusted relative risk [aRR], 1.28 [95% CI, 1.20 to 1.38]), physical health and well-being (aRR, 1.28 [95% CI, 1.20 to 1.36]), and emotional maturity (aRR, 1.27 [95% CI, 1.18 to 1.37]).[22]

Anxiety

We found no recent estimates of the prevalence of anxiety disorders among adults in the US. In 2001-2004, an estimated 19.1 percent of adults had an anxiety disorder in the past year, according to the National Comorbidity Survey-Replication study (**Table 2**).[23] The lifetime prevalence of anxiety disorders in adults in the US is 40.4 percent for women and 26.4 percent for men, according to data collected in 2001-2002.[24] More recent data from the 2019 National Health Interview Survey focus on the presence of generalized anxiety disorder (GAD) symptoms according to the GAD-7 screening questionnaire, and found that 9.5%, 3.4%, and 2.7% of adults had experienced mild, moderate, or severe symptoms of anxiety in the past 2 weeks, respectively.[25] According to this survey, anxiety symptoms were highest among those aged 18–29 and decreased with age, and were higher in women than in men. Asian-American adults were least likely to experience anxiety symptoms compared with Hispanic, non-Hispanic White, and non-Hispanic Black adults. Perinatal GAD has an estimated prevalence of 8.5 percent–10.5 percent during pregnancy and 4.4 percent–10.8 percent postpartum.[26] During August 2020-February 2021, the percentage of adults with recent symptoms of an anxiety or a depressive disorder increased from 36.4 percent to 41.5 percent.[27]

Anxiety disorders are associated with impaired quality of life[28] and functioning,[29] and substantial economic costs.[30] One review estimated average health expenditures attributable to anxiety disorders among countries in the Organization for Economic Cooperation and Development (OECD) to be $135 billion.[31] A meta-analysis indicated that anxiety disorders are a statistically significant, albeit weak, predictor of suicide ideation and attempts.[32] According to the Global Burden of Disease study, anxiety disorders were the sixth leading cause of disability in high income countries in 2010.[33] A prospective examination of data from the 2011 National Health and Aging Trends Study found that depression and anxiety symptoms in adults without disability or impairments were prospectively associated with disability and impairments in self-care and household activities 5 years later.[34, 35] A large retrospective cohort study of the impact of anxiety disorders during pregnancy found that anxiety was an independent risk factor for preterm delivery (adjusted OR 1.8, 95% CI 1.32-2.69; $P < 0.001$), hypertensive disorders during pregnancy (adjusted OR 1.7, 95% CI 1.08-2.69; $P = 0.02$) and cesarean delivery (adjusted OR 1.6, 95% CI 1.32-2.1; $P < 0.001$).[36] Perinatal anxiety can potentially impact mother–infant bonding and influence neurodevelopmental outcomes in children,[26] and offspring born to mothers with anxiety disorders during pregnancy had higher rates of neuropsychiatric-related hospitalizations (6.3 vs 3.1% $P = 0.002$; Kaplan-Meier log-rank test $P < 0.001$).[36]

Suicide Risk

In 2019, a total of 47,511 deaths were attributable to suicide (**Table 3**).[37] Suicide was the tenth leading cause of death in adults in 2019, accounting for 45,861 deaths.[38] In the same year, an estimated 381,295 adults visited hospital emergency department for nonfatal, self-inflicted injuries. From 2001 to 2017, there was a 31 percent increase in the number of suicide deaths in the US.[39] Overall rates flattened and even declined[40] in recent years; provisional suicide counts in 2020 numbered 45,855, which was 3% less than in 2019 (47,511).[41] However, rates did not decline among Black and Hispanic persons.[42] In 2017, suicide accounted for over 1.8 million years of potential life lost (YPLL) before the age of 85 years—nearly five percent of total YPLL

in the US.[43] Disorders that most strongly predict suicide attempts are bipolar disorder, PTSD, and MDD; the increased risk of suicide attempts for people with these disorders appears to be mediated by the increased risk of suicidal ideation with these disorders.[44] Additionally, hopelessness is predictive of suicide and suicide attempts among those with suicidal ideation, but research has not supported impulsivity as a predictor of suicide attempts.[44]

Men are more than three times more likely to die from suicide than women.[45] The highest suicide rates for women occur between the ages of 45 and 54 years, while for men the highest rates are over age 65 years.[39] Suicide rates vary by race. In the US, the highest age-adjusted suicide rates are among adults who are White, followed by American Indians and Alaska Natives.[45] From 2018-2019, the overall age-adjusted rates of suicide decreased for White and American Indian or Alaska Native individuals; however, between 2014 and 2019 the age-adjusted rate increased for Black individuals by 30 percent, and Asian or Pacific Islander individuals by 16 percent.[46] Military veterans are 1.5 times more likely to die by suicide than non-veteran adults, and that rate is even higher for female veterans.[47] However, veterans are not more likely to report suicide attempts or suicidal ideation compared to nonveterans.[2] A similar pattern of risk is seen for suicide attempts. A recent analysis exploring suicide risk during the years 2008-2019 indicate the following relative increased risks for suicide attempts: serious psychological distress (aOR, 7.51 [95% CI, 6.49-8.68]; P < .001), major depressive episodes (aOR, 2.90 [95% CI, 2.57-3.27]; P < .001), alcohol use disorder (aOR, 1.81 [95%CI, 1.61-2.04]; P< .001), divorced or separated (aOR, 1.65 [95% CI, 1.35-2.02]; P < .001), unemployed (aOR, 1.47 [95% CI, 1.27-1.70]; P< .001), identified as Black (aOR, 1.41 [95% CI, 1.24-1.60]; P < .001), identified as American Indian or Alaska Native, Asian, or Native Hawaiian or Other Pacific Islander (aOR, 1.56 [95% CI, 1.26-1.93]; P < .001).[48]

According to data from the National Survey on Drug Use and Health during years 2015-2019, 4.3 percent of US adults (10.6 million (annual average)) reported having suicidal thoughts during the previous year.[38]Additionally, an estimated 1.3 percent of adults (3.1 million adults) in the US made suicide plans and 0.6 percent (1.4 million) attempted suicide (**Table 4**).[38, 49] Female adults when compared with male adults, and younger adults (aged 18-39) compared with adults at or older than 40 were more likely than males to have suicidal thoughts, made plans to kill themselves, or attempted suicide in the past year.[38]An estimated 381,295 adults visited hospital emergency department for nonfatal, self-inflicted injuries.[38] The cost for suicides and suicide attempts in the US in 2013 was estimated at $58.4 billion, including lost productivity costs.[50]

Etiology and Natural History

Depression

The causes of depression are likely multifactorial, including both biological and environmental factors.[51] The onset of depression can occur at any age, but most frequently begins in adolescence or early adulthood.[52, 53] Experiencing trauma or adverse life events increases the likelihood of developing depression, though underlying biology may predispose persons affected by environmental stimuli, such as life events, to a greater or lesser extent.[54, 55] It is also suspected that heritability is a factor in developing depression: first-degree relatives of individuals diagnosed with depression have a two- to three-times greater risk of developing depression

compared to the general population.[56] Additionally, several twin studies and family cohorts have estimated the heritability of depression, though these studies offer only associational insights.[57] Other risk factors for developing depression include a history of childhood sexual abuse,[58] intimate partner violence,[59] comorbid mental health diagnoses, substance abuse, and certain illnesses, such as stroke and cardiovascular disease events.[60] Some medications, such as hormonal contraception and β-blockers, may also increase one's risk of developing depression.[61, 62] Among older adults social isolation is in important risk factor for depression and other mental health concerns.[63] Risk factors for perinatal depression include stress, lack of social support, current or past abuse, history of depression, and marital or partner dissatisfaction.[64]

In addition, structural inequities that disadvantage Black, Hispanic, and Native American families are numerous. Examples include housing policies (e.g., redlining, home loan financing), drug and criminal justice policies (e.g., treatment of crack versus power cocaine), employment policies (e.g., exclusion of agricultural and domestic workers from unemployment and retirement benefits) and disinvestment in communities with a high proportion of Black, Hispanic, and Native American residents.[65] Challenges posed by structural inequities and by the resulting income inequalities have a damaging impact on mental health in disadvantaged communities, and have been specifically correlated with depression prevalence,[66, 67] For example, unemployment, precarious employment, low income, race/ethnicity, immigrant status, sexual orientation, and/or occupational status have all been associated with higher risk of depression.[68] Interestingly, evidence based on the National Survey of American Life suggests that race, gender, income, and education interact as risk and protective factors for depression.[69] This study found that white women benefit more from income, Black women benefit from education, but high income (above and beyond education, employment, and marital status) may become a risk factor for Black men.

The COVID-19 pandemic and increasing numbers of serious natural disasters affecting the US have had an important impact on mental health. A 2020 review concluded that the psychological effects of the current pandemic as well as past epidemics and natural disasters suggest numerous psychological impacts.[70] Alcohol use, PTSD, anxiety, anger, fear of contagion, perceived risk, uncertainty, and distrust are a few of the immediate and long-term effects that are likely to result from the COVID-19 pandemic.

Depression can be a chronic condition and is characterized by periods of remission and recurrence of various lengths, though this varies individually.[71] Severity of depression at diagnosis may influence time to remission or relapse rate after treatment, with moderate to severe depressive episodes being slower to remit.[72] Level of functioning, comorbidities, and adherence to treatment also play a role in recovery rates.[73] Some people do fully recover. A community survey of Canadian adults found that, among those with a history of depression, 39 percent met the study's definition of complete mental health, which included the presence of happiness or life satisfaction and social and psychological well-being, as well as the absence of mental health disorders.[74]

Anxiety

Anxiety disorders often have onset during childhood and adolescence, with a median age of onset of 11 years.[75] Prevalence of anxiety disorders tends to decrease in the middle and older adult years, and is the lowest among those age 65 to 79.[75] The lifetime prevalence of anxiety disorders in adulthood is higher for women (40.4%) than men (26.4%).[24] Risk factors for anxiety disorders in adults are wide-ranging and include sociodemographic factors (female sex, non-Hispanic ethnicity, African-American race, marital status of widowed or divorced, economic deprivation), psychosocial factors (stressful life events, smoking and alcohol use), and physical and mental health factors (presence of other mental health conditions, parental history of mental disorders).[76] In addition, anxiety and depression strongly overlap. One cohort study found that 67 percent of individuals with a depressive disorder also had a current anxiety disorder, and 75 percent had a lifetime comorbid anxiety disorder.[77] Like depression, the course of anxiety tends to be chronic,[75] yet some people do recover. Similar to the findings for depression, 40 percent of adults with a history of generalized anxiety disorder who completed a Canadian community survey met the study's definition of complete mental health.[78]

Suicide

Suicide death is very rare prior to adolescence.[39] Regardless, it is the second-leading cause of death in age groups 10 to 34 years of age.[23] Many young adults experience suicidal thoughts—in 2017, 10.5 percent of young adults age 18 to 25 experienced suicidal thoughts in the US, and 1.9 percent attempted suicide.[23] A previous suicide attempt is the strongest predictor of future suicide death.[79] Suicide and suicide behavior are complex and predictors are multifactorial, and models have been developed to attempt to describe various factors and pathways.[44, 80] A wide range of risk factors are associated with suicide, including the presence of depression, other mental health disorders, and substance abuse; family history of mental health disorders, substance abuse, or suicide; certain medical conditions; chronic pain; family violence or abuse; having firearms in the home; and recent incarceration.[81] A study that examined the medical charts of 157 people who had died by suicide indicated that 70 percent or more had each of the following risk factors: prior suicidal ideation or suicide attempt; anxiety or agitation; sleep problems; current strain related to intimate partner, job, or finances; a mood disorder diagnosis; and had acquired the means for suicide.[82] A separate study of 421 people who had died during pregnancy determined that, among persons who died by suicide during pregnancy, 72% had a history of depression.[83]

Rationale for Screening

Depression and anxiety are relatively common, a source of tremendous suffering, are often unrecognized in primary care settings,[84, 85] and years-long delays in treatment initiation are the norm.[86] If effective, routine screening could substantially increase the likelihood that patients receive treatment, potentially saving years of suffering and reducing economic burden. While suicide is rare, it is catastrophic and in many cases likely preventable.[7] From 2008 through 2019, 34.8 percent to 45.5 percent of adults with a suicide attempt reported needing services but did not receive them, with no significant change from 2008 to 2019.[48] Screening has the potential to

substantially increase identification of patients in need of further evaluation and referral to treatment and may prevent suicide deaths.

Screening Strategies

Screening for mental health conditions involves administration of brief questionnaires to determine whether people have been experiencing mental health symptoms. Thus, patients who screen positive are not asymptomatic but rather have symptoms that have not been detected by the healthcare clinician. Many brief screening tools have been developed that may be used to screen for depression, anxiety, or suicide risk and are appropriate for use in primary care. For all conditions, rather than assigning a diagnosis based on a positive screening test, patients who screen positive should receive a more thorough assessment to determine symptom severity, whether a mental health condition is present, the need for treatment, patient treatment history and preferences, and the most important impacts of the condition for the patient.

Potential barriers to implementation of screening include provider knowledge and comfort level with screening, provider access to effective screening instruments, and impact on care flow. In addition, a trusting relationship with a clinician who is sensitive to cultural issues and free of implicit bias is an important part of effective mental health screening and accurate diagnosis. Implicit bias may be reflected, for example, by the fact that Black adults have a higher rate of being diagnosed with schizophrenia,[87] a phenomena that has been documented across approximately 30 years. One group of researchers found evidence to support a pattern of under-recognition of mood-related symptoms and over-emphasis of psychotic-spectrum symptoms, suggesting racial bias in the diagnosis of schizophrenia spectrum disorders that might also contribute to underdiagnosis of mood disorders.[88, 89]Other evidence suggests a tendency for differences in symptom presentation across racial and ethnic groups, highlighting the need for cultural sensitivity.[90, 91] See Appendix H for a more extensive discussion of racial and ethnic differences in diagnosis and presentation.

We have identified selected tools that appear to be most widely used or recommended for use in the US (**Table 5**)[92-96]. Some of these tools were not specifically designed for screening, but were developed for purposes such as supporting diagnosis, assessing severity, or monitoring treatment response, but may be feasible as screening tools.

Treatment Approaches, First-Line Treatments

Identification of mental health conditions alone is not always sufficient to ensure effective treatment in primary care settings. Rather, successful treatment requires a number of steps, including recognition that a patient is depressed, treatment initiation (often including referral and care coordination), and completion of an adequate course of treatment.[97]

First-line treatments for all of these disorders include psychotherapy (e.g., cognitive behavioral, interpersonal, family, and acceptance and commitment therapy) and pharmacotherapy (e.g., antidepressants, see **Table 6**).[98-100] Anxiety treatment may also include focused work on relaxation and desensitization, and some medications that are specific to anxiety (e.g.,

benzodiazepines). Interventions developed for people at high risk of suicide can include dialectical behavioral therapy, cognitive behavioral therapy for suicide prevention (CT-SP), and collaborative assessment and management of suicide risk (CAMS).[44] Interventions for those at high risk of suicide may include suicide-specific components such as safety assessment, means restriction, and pharmacological agents that may be specifically directed at suicide risk (e.g., lithium) as well as psychological and pharmacologic treatment aimed at underlying mental health conditions. Dialectical behavior therapy is a variant of cognitive behavioral therapy that has been used in patient populations at high risk of suicide, particularly those diagnosed with Borderline Personality Disorder.[101, 102]

Given the high degree of overlap between depression and anxiety, transdiagnostic approaches have been developed for use with patients who have either or both conditions. This approach focuses on identifying common maladaptive psychological, cognitive, emotional, interpersonal, and behavioral processes that underpin a broad array of mental health challenges.[103] This approach is consistent with the Research Domain Criteria (RDC) promoted by the National Institute for Mental Health that focuses on underlying mechanisms related to mental health (e.g., cognition, negative affect, arousal) rather than focusing ICD or DSM diagnosis.[104]

Current Clinical Practice in the United States and Recent Recommendations

Despite the USPSTF recommendation to screen for depression, data from a nationally representative survey of adults ages 35 and older conducted in 2014 and 2015 indicated that only 49 percent had been screened or assessed for depression at a routine health care visit in the past year (i.e., agreed that a health care professional had asked them about their mood, "such as whether you are anxious or depressed").[105] Adults who were males, older than age 75 years, uninsured, Black, of Asian or Hispanic ethnicity, and who had lower educational attainment were less likely to have been screened than their counterparts in this study. Screening rates are much lower when based on medical records documentation. Data from the 2012 and 2013 National Ambulatory Medical Care Survey (NAMCS) found that only 4.2 percent of adults without known existing depression were screened for depression at primary care visits.[106] During perinatal care visits, 79.1 percent of women reported that a health care provider asked about depression, and 87.4 percent of women reported that a provider asked about depression during postpartum visits.[9]

Depression screening rates do appear to be increasing, however, since the USPSTF initially issued its B recommendation to screen in 2009. An analysis of NAMCS data from 2005 through 2015 found that screening rates among adults without a known depression diagnosis who made an ambulatory care visit to a non-psychiatrist steadily increased from a low of 0.65 percent in 2008 (one year prior to first USPSTF recommendation to screen adults for depression) to 3.0 percent in 2015.[107] In the absence of screening, it is estimated that only 50 percent of patients with major depression are identified.[84] Depression is undiagnosed in pregnant women who have experienced a major depressive episodes more often than in nonpregnant women of reproductive age (66% undiagnosed vs. 59%), despite having more frequent contact with the healthcare system.[108] According to the World Health Organization's World Mental Health Initiative, only

35 percent of adults in the US with a depressive disorder initiated treatment in the first year of depression onset, and the median time to treatment initiation was 4.0 years.[86]

We did not find information on screening rates for anxiety and suicide risk. Anxiety disorders do not appear to be regularly screened for in most U.S. primary care settings, and under-detection appears to be common. For example, one study of primary care patients in Quebec, Canada found that only 52.5 percent of primary care patients with generalized anxiety disorder were recognized as having the disorder.[85] Under-detection may be related to the fact that patients with anxiety disorders often present with other complaints. For example, one study found that only 13.3 percent of primary care patients with generalized anxiety disorder presented with anxiety as the chief complaint; more common complaints in these patients were somatic complaints (47.8%), pain (34.7%), and sleep disturbance (32.5%).[109] Delays in treatment initiation appear even more pronounced than for depressive disorders: according to the World Mental Health Initiative, only 11 percent of American adults with an anxiety disorder initiated treatment within the first year of onset, and the median time to treatment initiation was 23.0 years.[86]

Suicide screening likely primarily occurs as part of depression screening, among settings that have implemented suicide screening. For example, the PHQ-9 includes an item on suicidal ideation, and an affirmative response to this item typically warrants followup that may include administration of a more extensive suicide risk assessment or instrument. It is unclear how frequently high suicide risk is detected in primary care, in the absence of routine screening. Only 36 percent of U.S. primary care providers discussed suicide in encounters with patients portraying major depression, adjustment disorder, or seeking antidepressants.[110] Further, one study found that as many as 83 percent of individuals who died by suicide had a health care visit in the prior year, yet only 24 percent had a mental health diagnosis in the four-week period prior to death. Together, these data indicate that primary care clinicians likely have underutilized opportunities to identify patients who are at a high risk of suicide.[111]

Even though individuals may be screened for depression and diagnosed, many do not receive adequate treatment. Less than half of people who experience a mental illness will receive mental health care.[112, 113] There are systemic barriers, such as lack of connection between mental health and primary care, as well as patient hesitation to initiate treatment and non-adherence to medication and therapy.[112, 114] For example, a study of 965 primary care patients in the U.S. found that only 41 percent of patients with an anxiety disorder were receiving treatment for their disorder.[29] We were unable to find information on treatment and referral rates for high suicide risk among patients identified in U.S.-based primary care settings.

Recommendations of Others

Several professional organizations recommend universal screening for depression in the general adult population.[115-119] However, the National Institute for Health and Care Excellence (NICE) recommends only that providers administer a brief, question-based screener to patients they suspect may have depression, and the Canadian Task Force on Preventive Health Care (CTFPHC) similarly recommends against routinely screening for depression in adults who are at average risk.[120, 121] The UK's National Screening Committee state that the reasons for not recommending depression screening include concerns about false positive screens, uncertainty as

to whether screening reduced depression, whether treatment of mild depression was effective, and concerns about how well depression is managed in the UK.[122] Screening for postpartum depression is recommended by several professional organizations.[5, 123, 124] The American College of Obstetricians and Gynecologists and the Center Of Perinatal Excellence also recommend anxiety screening for perinatal[124] or postpartum[5] women, however NICE again recommends only that clinicians be alert to the possibility of anxiety disorders rather than recommending broad routine screening.[125] The Women's Preventive Services Initiative (WPSI) recommends that screening for anxiety should include all female patients aged 13 years and older not currently diagnosed with anxiety disorders, including pregnant and postpartum women.[126] Both the Department of Veterans Affairs and the Canadian Coalition for Seniors' Mental Health recommended regular screening for suicide risk.[127-129] The Michigan Quality Improvement Consortium recommends suicide screening only for individuals diagnosed with depressive disorders.[130] See **Table 7** for a brief description of these and other relevant guidelines.

In addition, Healthy People 2030[131] has a number of objectives relevant to this review, including:

- Increase the proportion of primary care visits where adolescents and adults are screened for depression (MHMD-08)
- Increase the proportion of women who get screened for postpartum depression (MICH-D01)
- Increase the proportion of adults with depression who get treatment (MHMD-05)
- Reduce the suicide rate (MHMD-01)
- Reduce emergency department visits for nonfatal intentional self-harm injuries (IVP-19)

The National Committee for Quality Assurance has also developed a number of measures related to depression screening and care for health plans.[132] Relevant Healthcare Effectiveness Data and Information Set (HEDIS) measures include:

- Depression Screening: The percentage of members who were screened for clinical depression using a standardized tool.
- Followup on Positive Screen: The percentage of members who screened positive for depression and received followup care within 30 days.
- Utilization of the PHQ-9 to Monitor Depression Symptoms for Adolescents and Adults: The percentage of members 12 years of age and older with a diagnosis of depression, who had an outpatient encounter with a PHQ-9 score present in their record in the same assessment period as the encounter.
- Depression Remission or Response for Adolescents and Adults: The percentage of members 12 years of age and older with a diagnosis of depression and an elevated PHQ-9 score, who had evidence of response or remission within 4–8 months of the elevated score.

Previous USPSTF Recommendations

In 2016, the USPSTF recommended screening for depression in the general adult population, including pregnant and postpartum women.[133] They further stated that screening should be

implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate followup. (**Grade B recommendation**).

In addition, the USPSTF has issued two other depression-related recommendations. In 2022, the USPSTF recommended screening for major depressive disorder in adolescents aged 12 to 18 years (**Grade B recommendation**).[134] They also concluded that the evidence was insufficient to recommend for or against depression screening in children age 11 and younger (**I statement**). In 2016, The USPSTF recommended that clinicians provide or refer pregnant and postpartum persons who are at increased risk of perinatal depression to preventive counseling interventions (**Grade B recommendation**).[135]

The USPSTF has never issued a recommendation on screening for anxiety disorders for adults, but in 2022 issued a recommendation to screen for anxiety disorders in young people age 8 to 18 years (**Grade B recommendation**).[136]

In 2014, the USPSTF concluded that the evidence was insufficient to assess the balance of benefits and harms associated with screening for suicide risk (**I statement**) in adolescents, adults, and older adults.[137] They came to the same conclusion for adolescents in 2022 (**I statement**).[134]

Chapter 2. Methods

Scope and Purpose

This new topic incorporates and updates the evidence related to screening for and treatment of depression[1] and suicide risk[2] while adding evidence related to screening for and treatment of anxiety disorders and combination approaches that address more than one of these conditions. In general, this review focuses on screening adults (age ≥19 years) in primary care, including pregnant and postpartum persons, for depressive disorders, anxiety disorders, or for being at high risk of suicide. The evidence related to screening in child and adolescent populations are addressed by a separate topic and will not be reviewed here.[138] This review provides updated and new evidence regarding the accuracy of instruments used to screen for depression, anxiety, or suicide risk in addition to the benefits and harms of screening and treatment for depression, anxiety, and the prevention of suicide. The USPSTF will use this review to update its 2016 recommendation on depression screening and 2014 recommendation on screening for suicide risk in primary care in the US,[133, 137] as well as consider a separate recommendation on screening for anxiety.

We generally kept a consistent framework across all conditions but used existing systematic reviews (ESRs) for large, mature bodies of evidence and primary studies for smaller bodies of evidence.

Key Questions and Analytic Framework

With input from the USPSTF, we developed an Analytic Framework (**Figure 1**) and five KQs, using the USPSTF's methods to guide the literature search, data abstraction, and data synthesis.

1. Do depression, anxiety, or suicide risk screening programs in primary care or comparable settings result in improved health outcomes in adults, including pregnant and postpartum persons?
    a. Does returning depression, anxiety, or suicide risk screening test results to providers (with or without additional care management supports) result in improved health outcomes?
2. Do instruments to screen for depression, anxiety, or high suicide risk accurately identify adults, including pregnant and postpartum persons, with depression, anxiety, and high suicide risk in primary care or comparable settings?
3. What are the harms associated with screening for depression, anxiety, or suicide risk in primary care or comparable settings in adults, including pregnant and postpartum persons?
4. Does treatment (i.e., psychotherapy, pharmacotherapy, or both) of depression, anxiety, or high suicide risk result in improved health outcomes in adults, including pregnant and postpartum persons?
5. What are the harms of treatment (i.e., psychotherapy, pharmacotherapy, or both) of depression, anxiety, or high suicide risk in adults, including pregnant and postpartum persons?

In addition, we delineated five contextual questions, which were addressed using abbreviated, not fully systematic methods and are therefore not shown on our analytic framework:

1. What is the differential effect of screening for depression, anxiety, or suicide risk separately compared with screening for one or more of these conditions at the same time?
2. Does screening improve process outcomes such as identification and appropriate diagnosis of persons with depression, anxiety, or risk of suicide; appropriate follow-up and referrals; mental health treatment engagement and retention?
3. What health care system supports (e.g., collaborative care) can help ensure appropriate diagnosis and followup, treatment engagement and retention, and improved outcomes?
4. How well do suicide risk screening instruments predict future suicide attempts?
5. What is known about the validity of the most commonly used or recommended instruments to screen for depression, anxiety, and suicide risk in U.S. racial or ethnic minority patients?

Data Sources and Searches

We worked with a research librarian to develop a search strategy designed to identify studies of screening or treatment of depression, anxiety, or suicide risk, as well as studies investigating the accuracy of instruments used to screen for these conditions (**Appendix A**). The search was peer-reviewed by a second research librarian and was executed on September 24, 2021, searching for English publications in the following databases: Ovid MEDLINE, the Cochrane Central Register of Controlled Clinical Trials, and PsycINFO. We conducted ongoing surveillance through January 21, 2022.

Due to the expanded scope and the incorporation of evidence from previous USPSTF reviews, the start dates varied by condition and KQ (**Appendix A Table 1**). For KQs 1, 2, and 3 for depression and suicide risk, we bridged the search from the previous reviews, from 2014 and 2012 respectively. For KQs 1 and 3 for anxiety, we determined the search start year as 1990 since most SSRIs were approved in the early 1990s. For test accuracy studies (KQ2) for anxiety, we started our search in 2014, bridging from previously identified ESRs. For KQs 4 and 5, we searched for ESRs of depression treatment starting in 2015, but also searched for earlier Cochrane reviews if an evidence gap was identified in the literature published in or after 2015. For anxiety treatment benefit and harms (KQs 4 and 5), we bridged from previously identified ESRs for primary studies, with a search start date of 2015 and reviewed primary studies and other ESRs for inclusion. For suicide risk (KQs 4 and 5), we bridged from the previous USPSTF review, using a search start date of 2012.

In addition to the KQ search, we examined the reference lists of other previously published reviews, meta-analyses, and primary studies to identify additional potential publications for inclusion. We supplemented our searches with suggestions from experts and articles identified through news and table-of-contents alerts. We also searched ClinicalTrials.gov (https://ClinicalTrials.gov/) for ongoing trials that were listed as “recruiting,” “active,” “not recruiting,” “not yet recruiting,” “completed,” or “terminated” to identify relevant studies underway.

We imported the literature from these sources directly into EndNote® X7 (Thomson Reuters, New York, NY).

Study Selection

Two reviewers independently screened titles and abstracts of all references identified in the searches, using the inclusion and exclusion criteria as a guide to identify eligible studies. We developed criteria for inclusion and exclusion of primary studies and systematic reviews for each KQ (**Appendix A Table 2**). Potentially relevant studies included based on title and abstract were then independently assessed by two reviewers at full text using a standard form that outlined eligibility criteria. Any disagreements were reconciled through discussion or consultation with a third reviewer. Study assessment was conducted in DistillerSR (Evidence Partners, Ottawa, Canada), where detailed records were kept of all included and excluded studies.

For KQs 1 and 3 (benefits and harms of screening), we included RCTs of primary care (or comparable broad healthcare-based) adult populations (age ≥19), including pregnant people, investigating the benefits or harms of brief screening interventions for depression, anxiety, or suicide risk. For KQ1, we included studies in which the control group was also screened, but the screening results were not given to the participants' primary care clinician (these were considered KQ1a studies). In addition, we included studies with additional components beyond screening, such as referral support, training in diagnosis or management, and patient materials.

For KQ 2 (test accuracy), we limited inclusion to only the most widely used or recommended screening tools for anxiety and depression but had no restriction on specific tools for suicide risk screening. For depression screening instruments, we included ESRs of the following tools: Patient Health Questionnaire (PHQ), any version; Center for Epidemiologic Studies Depression Scale (CES-D); Edinburgh Postpartum Depression Scale (EPDS) for perinatal persons. We additionally included any primary studies of the Geriatric Depression Scale (GDS) for older adults. For anxiety, we included primary studies for the following screening instruments: Generalized Anxiety Disorder scale (GAD), in any form; PHQ Anxiety scale; EPDS-Anxiety subscale, for perinatal persons; Geriatric Anxiety Inventory (GAI) and Geriatric Anxiety Scale (GAS) for older adults. For suicide screening, we included primary studies of any brief tools. **Appendix A Tables 3–12** provide an overview of the included screening instruments for KQ2.

For KQ4 and 5 (benefits and harms of treatment) of anxiety and suicide risk, we included RCTs of psychological, pharmacological, or combination interventions compared to control conditions (e.g., placebo, usual care, wait list or attention control conditions). For anxiety and suicide risk we planned to initially limit inclusion to RCTs in which participants were recruited from a primary care or comparable health care settings. If evidence was insufficient when limited to primary care-based recruitment, we planned to expand the scope to include recruitment from other non-acute settings for suicide prevention treatment (e.g., recruitment from mental health settings), and to expanded to include ESRs of treatment for anxiety. In both cases, the primary care-based evidence was limited so we expanded our scope as planned. For the benefits and harms of anxiety treatment, we included only ESR results from broad analyses (e.g., not broken down or limited by intervention type or format, specific measures, or type of control group) and

limited the examination of effect modification to publication bias and study quality/risk of bias. For the benefits and harms of suicide prevention treatment, we excluded studies that recruited patients from emergency or inpatient settings who were in the midst of an acute suicidal crisis, due to limited applicability of the findings to patients who would be identified through screening in primary care settings. For all conditions we excluded studies *limited to* people with comorbid medical and mental health conditions such as cancer, cardiovascular disease, substance use disorders, and serious mental illnesses.

We used ESRs to address the benefits (KQ4) and harms (KQ5) of psychological, pharmacological, and combined treatment of depression, due to the extremely large volume of literature and the maturity of the evidence base. Given the large number of reviews that met our eligibility criteria for these KQs, we adapted the decision tool developed by Pollack and colleagues[139] to identify the most current and comprehensive evidence. As per Pollack and colleagues methods, we first focused on Cochrane reviews, followed by reviewing non-overlapping, non-Cochrane reviews.[139] Our adaptation was that for ESRs of psychological treatment, rather than focusing on Cochrane reviews, we focused first on ESRs utilizing a comprehensive database of studies of the psychological treatment of depression developed and maintained by Cuijpers and colleagues.[140] The Cuijpers database used a comprehensive search strategy and transparent, standardized methods for data extraction and coding, risk of bias assessment, and effect size calculation,[140] and incorporated more contemporary trials than Cochrane reviews for this body of literature. This database is updated annually. Among the reviews based on the Cuijpers database, we used only the most recently reported effect size for any outcome or analysis. Outside of Cochrane and Cuijpers ESRs, we included only the most comprehensive or recent ESR when multiple relevant reviews covered the same outcome for the same body of literature. For analyses examining effects in specific populations, we focused on analyses of groups based on age, sex or gender, race or ethnicity, sexual orientation, and socioeconomic status.

Finally, for harms of pharmacologic treatment (KQ5) of anxiety and depression, we also included large observational studies published after the search window of ESRs that included observational studies. We only included observational studies addressing serious harms, including death, suicide attempts, and events likely to require medical treatment.

Quality Assessment and Data Abstraction

We used several tools to assess and rate the credibility of both primary studies and ESRs under consideration for inclusion (**Appendix A Table 13**).

We used study quality rating standards from the USPSTF manual.[141] For primary research, two reviewers independently rated the studies' methodological quality using USPSTF design-specific criteria (**Appendix A Table 13**).[141] Studies were rated as "good," "fair," or "poor," and discrepancies between raters were resolved by discussion or consultation with the larger review team. Good-quality studies were those that met nearly all of the specified quality criteria (e.g., comparable groups were assembled initially and maintained throughout the study and followup was approximately 90% or higher). Because mental health outcomes are assessed through patient

self-report, good quality studies used either blinded, structured interviews or questionnaires completed without an interviewer's assistance. Fair-quality studies did not meet these criteria but did not have serious threats to their internal validity related to their design, execution, or reporting. Poor-quality studies typically had several important limitations, including at least one of the following risks of bias: very high attrition (generally >40%), differential attrition between intervention arms (generally >20%); substantial lack of baseline comparability between groups without adjustment; or issues in trial conduct, analysis, or reporting of results (e.g., possible selective reporting, inappropriate exclusion of participants from analyses, questionable validity of randomization and allocation concealment procedures, or data for relevant outcomes not collected systematically). Studies rated as poor quality were excluded from the review.

ESRs of benefits and harms of treatment were rated as "good" if they were recent, relevant reviews with comprehensive sources and search strategies; had explicit and relevant selection criteria; reported a standard appraisal of included studies; and had valid conclusions. We rated them as "fair" if they were not clearly biased but lacked comprehensive sources or search strategies or did not report a standard appraisal of included studies, but these limitations seemed unlikely to introduce bias for the aim of the specific review. For example, some individual patient data meta-analyses relied on sources such as studies in a registry or submitted to the FDA, with the goal of examining effect modification (rather than searching multiple databases as would typically be expected). Also, individual patient data meta-analyses generally did not report a standard appraisal of the included studies, but we considered them likely unbiased for their purpose of examining effect modification. Similarly, ESRs using a cohort of studies based on an FDA database to examine publication bias were included even if they did not report standard appraisal of the included studies. We assigned a "poor" rating and excluded ESRs that were outdated, irrelevant, or biased, without comprehensive and systematic search for studies, explicit selection criteria, or, with the exceptions noted above, standard appraisal of studies. For ESRs, a single reviewer conducted the quality assessment and only ESRs that were rated as poor quality by the first rater were rated by a second reviewer. Discrepancies were resolved by discussion or consultation with the larger review team.

For instrument accuracy studies, we used ROBIS[142] to evaluate the risk of bias for ESRs, and QUADAS-2[143] to evaluate the risk of bias of primary diagnostic accuracy studies. We ultimately rated studies and ESRs as "good", "fair", or "poor" quality. Studies and ESRs were evaluated independently by two reviewers, and if deemed by both reviewers to have a high risk of bias, they were rated "poor" and excluded.

We abstracted data from each included review and primary study into detailed abstraction forms using DistillerSR (Evidence Partners, Ottawa, Canada). For all included evidence, one reviewer completed primary data abstraction, and a second reviewer checked all data for accuracy and completeness.

For ESRs we abstracted aim, inclusion criteria, and detailed results for the main findings of outcomes included in our Research Plan. We stratified results for specific populations listed in the Research Plan for the outcome of depression symptoms (i.e., pregnant and postpartum persons, older adults, and individuals identified through population-based screening in primary care or comparable community settings, and subgroups based on age, sex or gender, race or

ethnicity, sexual orientation, and socioeconomic status). For other outcomes, stratified analyses were narratively summarized. Similarly, detailed results for effect modification analyses were only abstracted for the outcome depression symptoms and were narratively summarized for other outcomes.

Data Synthesis and Analysis

We synthesized findings using text, tables, and figures; where possible we conducted quantitative syntheses with meta-analysis. We used Stata 16.1 (StataCorp LLC, College Station, TX). All significance testing was 2-sided, and results were considered statistically significant if the p-value was 0.05 or less.

For meta-analysis of primary research trials (KQ1, KQ4), we used the restricted maximum likelihood model with the Knapp-Hartung correction for small numbers of studies.[144, 145] When studies included multiple intervention groups, we used the single most intensive or comprehensive intervention group per study in the meta-analysis. For dichotomous outcomes, we used study-reported adjusted risk rations (RRs) if available and calculated unadjusted RRs if adjusted results were not reported. For continuous measures, we used change from baseline in each group as the measure for analysis. We pooled between-group standardized mean differences (Hedges' g) because studies used a variety of specific measures. Where there was evidence of effect modification, our primary analyses were stratified by study population.

For meta-analysis of KQ2, data from 2-by-2 contingency tables were analyzed using a bivariate model, which modeled sensitivity and specificity simultaneously. If there were not enough studies to use the bivariate model, sensitivity and specificity were pooled separately, using random effects models with the DerSimonian & Laird method.[146] We did not quantitatively pool results when data were limited to fewer than three studies. When quantitative analyses were not possible, we used summary tables and forest plots to provide a graphical summary of results. For KQ2 studies that only conducted reference standard interviews with a subset of participants who screened negative, we extrapolated based on the proportions in the subgroup that met the diagnostic criteria to estimate sensitivity and specificity of the full sample.

For all meta-analysis, we assessed the presence of statistical heterogeneity among the studies using the I^2 statistic. When analyses found large statistical heterogeneity, we suggest using the 95% CI or range of estimates across the individual studies as opposed to point estimates. However, the high statistical heterogeneity for specificity is in partly due to the high degree of precision around estimates from individual studies.

For evidence from ESRs, we display pooled results in forest plots as reported in the ESRs. We used placebo-controlled comparisons if available. We accepted only RCT evidence for benefits of treatment (KQ4), but both RCT and observational evidence were eligible for harms of pharmacotherapy (KQ5). For results derived from observational studies, a parenthetical note is included in the forest plot.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each KQ within each condition. We adapted the Evidence-based Practice Center (EPC) approach,[147] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation Working Group.[148] Our method explicitly addresses four of the five EPC-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations). We did not address the fifth required domain—directness—as it is implied in the structure of the KQs (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). The body-of-evidence limitations reflect potential reporting bias, quality of the individual studies, and other important restrictions in answering the overall KQ (e.g., lack of replication of interventions, nonreporting of outcomes important to patients).

We graded the overall strength of evidence as high, moderate, or low. "High" indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effects. "Moderate" indicates moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate. "Low" indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. A grade of "insufficient" indicates that evidence is either unavailable or does not permit estimation of an effect. We developed our overall strength-of-evidence grade based on consensus discussion involving at least two reviewers.

Expert Review and Public Comment

A draft Research Plan was posted on the USPSTF Web site for public comment from May 7 to June 3, 2020. The USPSTF received comments regarding eligible populations, examination of subpopulations, outcomes, eligible settings, and requests for clarifications of language or approach. Commenters requested the inclusion of studies limited to persons with disabilities, medical conditions, and mental health conditions other than depression, anxiety, and increased suicide risk. In response to public comment, the USPSTF included studies that enroll participants with the conditions listed above; however, studies *limited to* participants with these conditions will not be included due to lack of broad applicability to primary care populations. Additionally, the USPSTF added a priori subpopulations of interest for detailed examination if data were available. Pregnancy outcomes were added, such as preterm birth, and a contextual question was added to address intermediate process outcomes such as appropriate diagnosis, treatment initiation, and treatment engagement. Another change in response to comments was the inclusion of studies in emergency department settings if the screening is broadly applied (e.g., not limited to persons in the midst of a mental health crisis). Finally, selected text was edited for clarity. In

addition, the draft evidence report was posted on the USPSTF Website for public comment from September 20 through October 18, 2022. In response to comments received, we corrected minor errors, adopted several suggested wording changes, provided some additional requested information or detail, and evaluated studies suggested for possible inclusion (but found that none met our inclusion criteria).

USPSTF Involvement

The authors worked with USPSTF at key points throughout the review process to develop and refine the analytic framework and key questions and to resolve issues pertaining to scope for the final evidence synthesis. This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. AHRQ staff provided oversight for the project, reviewed the draft report, and facilitated external review of the draft evidence synthesis. However, the authors are solely responsible for the content.

Chapter 3. Results

Overview of Included Studies

The results for this review will be presented by condition: depression, anxiety, and suicide risk. Within each condition, results are organized by KQ.

We reviewed 23,497 abstracts and assessed 1237 full-text articles for inclusion (**Appendix B Figure 1**). Overall, we included 185 original research studies or ESRs (reported in 231 publications) across conditions and KQs. This includes 99 primary studies and 86 existing systematic reviews, which collectively include approximately 5000 studies and 10.6 million participants (**Figure 2**). For depression we included a total of 105 studies [32 original studies (n=385,607) and 73 ESRs (including approximately 2,138 studies and an estimated 9.8 million participants), including the following: KQ1 included 17 RCTs, KQ2 included 14 primary studies and 10 ESRs; KQ3 included 1 RCT, KQ4 included 39 ESRs, and KQ5 included 27 ESRs (reported in 34 publications) and 1 cohort study. For anxiety, we included 59 studies [40 original studies (n=275,489) and 19 ESRs (including approximately 483 studies and an estimated 81,507 participants)] including the following: KQ1 included 2 RCTs, KQ2 included 10 studies, KQ3 had no included studies, KQ4 included 26 primary studies and 18 ESRs, and KQ5 included 3 RCTs, 8 ESRs, and 2 case-control studies. For suicide risk, we included 27 original studies (n=24,826), including the following: For KQ1, we included 1 RCT, KQ2 included 3 primary studies, KQ3 included 1 RCT, KQ4 included 23 RCTs, KQ5 had no additional included studies. The full lists of included studies (by condition) and excluded studies (with reasons for exclusion) are available in **Appendix C** and **Appendix D**, respectively.

Depression

KQ1. Do Depression Screening Programs in Primary Care or Comparable Settings Result in Improved Health Outcomes in Adults, Including Pregnant and Postpartum Persons?

KQ1a. Does Sending Depression Screening Test Results to Providers (With or Without Additional Care Management Supports) Result in Improved Health Outcomes?

Summary

Seventeen trials (reported in 28 publications) examined depression screening,[149-164] including one that examined screening for depression and several other conditions[165] (**Table 8**). The included trials covered general adult,[149-153, 165] older adult,[154-157] and perinatal populations.[158-164] Evidence supported the benefits of screening for depression (**Table 9**). For example, screening interventions, most of which also included other care management components, were associated

with a lower prevalence of depression or clinically important depressive symptomatology (OR, 0.60 [95% CI, 0.50 to 0.73]; 8 RCTs [n=10,244]; I^2=0%), and, among participants above a specified symptom level at baseline, a greater likelihood of remission or falling below a specified level of depression symptomatology (OR, 1.58 [95% CI, 1.23 to 2.02]; 8 RCTs [n=2,302]; I^2=0%) at 6 months post-baseline or postpartum (or the closest followup to 6 months).

Study Characteristics

Seventeen studies (n=18,437) examined the benefits of screening for depression,[149-165] including one that also screened for symptoms of anxiety, sleep problems, pain, or fatigue and enrolled patients endorsing any of these concerns (**Table 8**). Six of the included studies covered general adult populations,[149-153, 165] four were limited to older adults,[154-157] six were limited to postpartum patients (generally between 2 and 12 weeks postpartum),[158-162, 164] and one was limited to pregnant patients.[163] Only four[153, 159, 160, 162] of the included studies had a control group that was not screened for depression and are considered KQ1 studies (**Figure 3**). The remaining studies screened all participants but only gave the screening results to clinicians of intervention group participants, meeting criteria for KQ1a. Studies meeting criteria for KQ1 and KQ1a are combined and not discussed separately. Nine[149-152, 154-157, 165] of the included studies only enrolled patients who screened positive for depression. The remaining eight studies included all patients, regardless of the depression screening results,[153, 158-164] including all of the studies conducted in perinatal populations. All of the studies used some type of individual outreach from a predefined pool of potentially eligible persons for study recruitment, typically patients who were visiting or were registered with participating clinicians or clinics; none relied on interested individuals to contact the study in order to join the study. All but two[162, 165] of the included studies were also included in the previous USPSTF review on screening for depression.[1]

Nine of the studies were conducted in the US,[149-153, 155, 157, 164] and the remaining were conducted in the UK (among postpartum patients),[160, 161] Hong Kong (among postpartum patients),[159] or Northern European countries (covering older adult,[154, 156] postpartum,[158, 162] and pregnant[163] patients). Only one of the studies conducted in the US was focused on a perinatal population, conducted among postpartum patients[164]; the remaining US-based studies covered general[149-153, 165] and older[155, 157] adult populations. All studies took place in primary care, general practice, OB-GYN, or other maternal/child wellness contexts.

Information about the included samples is summarized in **Table 10** (see **Appendix E Table 1** for details by study). Across all 17 studies, the average age of participants was 38.2 and this varied by target population. Ninety-three percent of all participants were women; and a majority were women even among studies focused on general adult populations (73% women) and older adults (66% women). Among the nine studies conducted in the US, the percent of participants who were Black ranged from 7.1 to 51.2 (among the six studies reporting), the percent who were Hispanic/Latino ranged from 4.5 to 59.3 (among four reporting), and the percent who were White ranged from 29 to 94.1 (among the six reporting). Only one study reported the percent of participants of Asian descent, and none reported the percent who were Native American or Alaska Native. Three studies had a relatively high proportion of Black participants, with 49.3 percent[165] (among a general adult population), 51.2 percent[155] (older adults), and 32.6 percent[157] (older adults). One study[153] had a relatively high proportion of Hispanic/Latino participants

(59.3%, general adult population). One study focused on primary care patients in rural clinics[149] and three had samples who were largely economically disadvantaged, as evidenced by being on Medicaid or uninsured and below the poverty line,[150] being medically indigent[155] or having low annual income levels (e.g., 76% earning less than $17,000 in the late 1990s).[153]

The included interventions were very heterogeneous (**Table 11, Appendix E Table 2**). Four trials studied the effects of screening (or receipt of screening results) with little or no further training or intervention components, conducted in general,[153, 149, 165] and postpartum[159] populations.[163] In these studies, primary care clinicians typically confirmed the diagnosis and made decisions about the need for treatment according to their usual approach. Additional components beyond screening variously offered in other studies included training and materials to improve clinicians' knowledge and skills surrounding diagnosis and treatment of depression, facilitation or improvement of the referral process, and patient-specific treatment recommendations based on screening results. Four studies offered one-on-one psychological counseling, medication adherence counseling, or symptom monitoring sessions by specially trained staff.[151, 152, 164, 156] Three of these included regular monitoring both of symptoms and medication use as well counseling sessions.[151, 152, 164]

Four studies were rated as good quality[151, 156, 165] and the remaining were rated as fair quality. The most common issue that warranted a "fair" rating was attrition higher than ten percent. Some fair-quality studies had few other concerns besides attrition (i.e., all or most of the following: adequate randomization methods, baseline comparability between groups, blinding of outcomes assessment, conservative handling of missing data, acceptable statistical methods, and no apparent selective reporting of outcomes).[152, 157, 161] Other common issues among fair-quality studies were lack of information about whether allocation was blinded and small sample sizes leading to uncertainty about baseline comparability between groups. One of the studies used a quasi-experimental design which assigned two comparable municipalities in Norway to be intervention and control areas,[158] but the remaining studies were either individual or cluster-randomized trials.

Results

Detailed results for all outcomes are reported in **Appendix E Tables**.

Depression Outcomes

Sixteen of the seventeen studies reported the percent of patients who (a) met criteria for a depression diagnosis or were above a specified symptom score at followup ("prevalence," **Appendix E Table 3**), (b) did not meet criteria for a depressive disorder or were below a specified symptom score at followup ("remission," **Appendix E Table 4**), or (c) showed a prespecified level of symptom reduction, such as a certain number of points or a percentage decline relative to their baseline score ("response," **Appendix E Table 5**). Pooled results for the first two of these are shown in **Table 9**. Pooled analyses showed that screening programs were associated with a lower prevalence of depression compared with no screening or no screening results being given to participants' clinicians (OR, 0.60 [95% CI, 0.50 to 0.73]; 8 RCTs [n=10,244]; I^2=0%), and, among participants above a specified symptom level at baseline, a

greater likelihood of remission (OR, 1.58 [95% CI, 1.23 to 2.02]; 8 RCTs [n=2,302]; I^2=0%) at 6 months post-baseline or 6 months postpartum (or the closest followup timepoint to 6 months). Absolute prevalence and remission rates were highly variable, presumably reflecting differences in how the outcome was measured and differences among the study samples. At followup, depression prevalence ranged from 2.5 percent to 67 percent in the control groups and from 0.6 percent to 62 percent in the intervention groups; the median (interquartile range) absolute difference in percentage points between groups was -5.2 (-6.8 to -2.0), favoring the screening groups. Depression remission ranged from 11.7 percent to 66 percent in the control groups and from 13.2 percent to 78.1 percent in the screening groups; the median (interquartile range) absolute difference in percentage points between groups was 7.2 (2.9 to 15.2), favoring the screening groups.

We also conducted a combined analysis, in which remission was entered if it was reported, prevalence (reversed) if remission was not reported, and the percent of participants meeting criteria for a "response" to treatment (typically 50% reduction in symptoms) if neither remission nor prevalence were reported (**Figure 4**). The combined analysis also demonstrated that the screening programs were associated with a 63 percent increase in the odds of improved depression (OR, 1.63 [95% CI, 1.37 to 1.95]; 16 RCTs [n=8,448]; I^2=0%). The most robust evidence is among general adult and postpartum populations. Only one trial was limited to pregnant persons, but those findings were consistent with the findings among general and postpartum populations. Among studies of general, postpartum, and pregnant patients, effect sizes were consistently in the direction of benefit, and many were statistically significant for at least one timepoint, particularly among perinatal women. The results in four trials limited to older adults (with lower age cutoffs ranging from 55 to 75 years) were inconsistent with point estimates on both sides of 1.0 and there were no studies reporting statistically significant differences between groups. Stratified analyses indicated statistically different pooled effects across populations and, in a separate analysis, that effect sizes were larger among trials that were not limited to people with symptoms of depression. These findings are discussed further below under "Effect modification and Findings in Specific Populations."

Thirteen studies also reported a continuous measure of the level of depression symptoms (**Figure 5**, **Appendix E Table 6**).[149-151, 154-161, 163, 165] All of the studies in perinatal patients reported greater reductions in depression symptoms in screening groups than the control groups at one or more time points.[158-161, 163] Differences between group were typically 1 to 3 points on the Edinburgh Postnatal Depression Scale (EPDS) at 6 to 26 weeks postpartum, and findings were statistically significant for one or more time points in all studies of perinatal women. Only one of the eight studies in non-perinatal populations found a statistically significantly greater reduction in depression symptoms,[151] although differences trended in the direction of a small benefit in most of the other studies. Several studies did not provide sufficiently detailed results for pooled analysis.

Other Mental Health Outcomes, Quality of Life, and Functioning

Some studies reported on anxiety (**Appendix E Table 7**),[161, 162, 165] broad mental health symptom levels (**Appendix E Table 7**),[159, 161] or quality of life (**Appendix E Table 8**).[150-152, 154, 156, 160-162] Consistent with the findings on depression symptoms, the studies limited to postpartum women

typically found small statistically significant benefits of the screening program, but the studies in general and older adults did not. One exception, however was that two studies in general adults with extensive screening supports both found improvements in mental health-related quality of life, as measure by the SF-36 mental health component scores.[151, 152] Two studies in older adults reported very similar effects on functioning in their screening and control groups (**Appendix E Table 9**).[154, 155]

Other Health Outcomes

One study of older adults reported all-cause mortality (**Appendix E Table 10**).[156] This study found fewer deaths in the screening group (5.8%) than in the control group (14.4%, OR, 0.36 [95% CI, 0.15-0.92]), however this was a small study with only 239 participants and 24 deaths. One study in postpartum women found no differences in the rate of hospitalization of their children or the child's body weight through age 18 months (**Appendix E Table 11**).[159]

Effect Modification and Findings in Specific Populations

No studies reported subgroup analyses exploring results by gender. Only one study each reported findings by age group (in a study limited to adults age 75 years and older[156]) and race/ethnicity.[152] No differential impact was identified for any outcome in either of these studies. Among studies that were limited to specific populations, stratified analyses of the combined depression outcome (i.e., including remission/below a cutoff, response, or prevalence/above a cutoff [reversed]) indicated statistically significant differences among the populations tested, with larger effects in studies limited to pregnant or postpartum patients ($p=0.005$), and smaller effects in studies limited to older adults ($p=0.007$). However, study design differed across populations, as well as other features, making it impossible to determine whether the population or the other study features drove the association with effect size. For example, studies in perinatal women were also more likely to include unscreened control groups and not to restrict their samples to patients with depressive symptoms, a factor that was also associated with larger effect sizes in stratified analyses ($p=0.01$). In addition, the relatively small number of included studies warrants caution in interpreting meta-analytic differences by study characteristics.

Effects in Older Adults

The trials among general adult populations included older adults but none of them reported subgroup effects by age. However, one of the trials in general adults had an average age of 58, indicating that a substantial minority were at least age 60 and older.[153] In this study, intervention group patients who were depressed at baseline were more likely to be in complete remission at followup than unscreened depressed patients. Specifically, 48 percent of screened participants had ≤ 1 symptom of depression compared to 27 percent of those not screened ($p<0.05$). Among the trials limited to older adults, only one used a measure of depression symptoms that was specifically designed for older adults.[157] This may be an important limitation because older adults commonly suffer from loss of energy, sleep disturbance, and other somatic symptoms of depression that are due to aging or medical conditions, so general symptom severity instruments may be less sensitive to treatment response. Additionally, none of the trials in older adults offered individual psychological counseling by someone with training in psychological treatment

in older adults, and the participation in psychoeducational groups offered in two studies was less than 20 percent in both cases.[156, 157] Thus, interventions in the studies of older adults fell almost entirely to the primary care provider.

KQ2. Do Instruments to Screen for Depression Accurately Identify Adults, Including Pregnant and Postpartum Persons, With Depression, in Primary Care or Comparable Settings?

Summary

We included 14 primary studies[166-179] and 10 existing systematic reviews (ESRs)[180-189] that examined the test accuracy of screening for depression (**Tables 12 and 13**). The 14 primary studies covered multiple versions of the Geriatric Depression Scale (GDS); the GDS-15 was the most common version. The standard cutoff of ≥5 (to identify mild to severe depression) had an acceptable balance of sensitivity and specificity with the GDS-15 accurately identifying 94 percent of those with major depression and 81 percent of those without (**Figure 6**).

The ESRs we identified covered various versions of the PHQ, 2- and 3-item Whooley screening questions, CES-D, and EPDS (**Figure 7**). The PHQ-9 correctly identified 85 percent of those with major depression and 85 percent of those without major depression, at the standard cutoff of ≥10, when compared to a semi-structured interview reference standard (**Figure 8**, for a more detailed depiction of the evidence). At the standard cutoff of ≥2 and when compared to a semi-structured interview, the PHQ-2 was more sensitive than the PHQ-9, correctly identifying 91 percent of people with major depression. But specificity at that cutoff was lower, accurately identifying only 67 percent of people without depression. The Whooley, CES-D, and EPDS demonstrated accuracy comparable to the PHQ-2.

Study Characteristics of Primary Research Studies

Fourteen primary studies (n=8819) were included that provided test accuracy results for the Geriatric Depression Scale (GDS, **Table 12**).[166-179] None of these studies were included in the previous review, as the previous review only addressed screening instrument accuracy for pregnant individuals. The GDS-15 was the most common version, but several other versions were also included. Two studies were conducted in the US.[167, 174] The others were conducted in Norway, Sweden, the Netherlands, the United Kingdom, Spain, Portugal, Romania, Australia, the Republic of Korea, and Singapore. Sample size ranged from 105 to 4,253; most studies (k=10) analyzed a sample of 500 participants or less.

Ten studies explicitly excluded those with cognitive impairment or those scoring low on cognitive function tests (e.g., MMSE) (**Table 12**). All studies recruited adults aged 55, 60, or 65 years and older or assisted living residents. Mean age ranged from 69 to 85 years (k=13) (**Table 14**). Women were represented in higher proportions than men: 50 to 77 percent of participants were women. Race and ethnicity were sparsely reported (k=4). One study conducted in Singapore recruited only participants of Chinese (90%) or Malaysian and South Asian Indian

(10%) ethnicity[168] and another study in the UK recruited only participants of African Caribbean ethnicity.[176] The two other studies reporting race or ethnicity recruited primarily White participants (85% and 90%).[167, 174] SES was variably reported; mean years of education ranged from 5.6 to 10 (k=3) and those with 12 or more years of education ranged from 65 to 69 percent (k=2).

All studies used a structured or semi-structured interview at no more than two weeks after the screener to diagnose depression. The most common interviews were the Structured Clinical Interview for DSM Disorders (SCID) (k=3), the Diagnostic Interview Schedule (DIS) (k=2), and the Mini International Neuropsychiatric Interview (MINI) (k=2); four studies did not report the specific interview used. The proportion of participants who were diagnosed with major depressive disorder ranged from 3.5 percent to 16.5 percent. Two studies did not use DSM to identify participants with major depression and instead defined depression as any symptom of depression based on ICD-10 (found in 10% of the sample)[170] and a depression score of 3 or more on the Geriatric Mental Scale (28.9%).[170, 176]

Results of Primary Research Studies

GDS-15

Thirteen studies reported the accuracy of GDS-15 to detect major depressive disorder or depression. Reported cutoffs ranged from ≥0 to ≥14, but the most common cutoff was ≥5 (k=8). The cutoff of ≥5 also had the best balance between sensitivity and specificity with a pooled sensitivity of 0.94 (95% CI, 0.85 to 0.98; I^2=84.4%; k=7; n=5,655) and pooled specificity of 0.81 (95% CI, 0.70 to 0.89; I^2=98.9%) to detect MDD (**Figure 6, Appendix E Table 12**). At a cutoff of ≥5, sensitivity from seven individual studies ranged from 0.72 to 1.0 and specificity ranged from 0.53 to 0.95. Area under the curve (AUC) for the GDS-15 was reported in eight studies and ranged from 0.79 (95% CI, 0.73 to 0.85) to 0.98 (95% CI, 0.97 to 0.99) (**Appendix E Table 12**).

One additional study—with an aim to estimate the prevalence of depression in the Netherlands—needed extrapolation of their random sample of participants screening negative back to the full screened sample.[173] After that adjustment, the study had the lowest sensitivity to detect MDD at a cutoff of ≥5: 0.58 (95% CI, 0.54 to 0.62). The corresponding specificity was 0.91 (95% CI, 0.90 to 0.91) (**Appendix Table C**). With this study included in the meta-analysis (k=8; n=11,095), at a cutoff of ≥5, the pooled sensitivity decreased and the pooled specificity increased: they were 0.92 (95% CI, 0.80 to 0.97; I^2=94.8%) and 0.83 (95% CI, 0.73 to 0.89; I^2=98.7%), respectively (pooled data not shown).

Lower cutoffs yielded higher sensitivity but lower specificity. Higher cutoffs were more variable but tended to yield higher specificities and lower sensitivities (**Figure 6, Appendix E Table 12**).

GDS-30

Four studies reported the accuracy of GDS-30 to detect major depressive disorder (MDD). Reported cutoffs ranged from ≥7 to ≥17 with only one cutoff used in more than one study (≥17). Sensitivity ranged from 0.55 at a cutoff of ≥11 to 1.0 at a cutoff of ≥15 and ≥17 (95% CI range,

0.38 to 1.0). Specificity was less variable and ranged from 0.67 at cutoff of ≥7 and ≥10 to 0.96 at a cutoff of ≥15 (95% CI range, 0.62 to 0.99) (**Appendix E Table 12**). With few studies and few cutoffs reported, a consistent relationship between cutoff and test performance was not identified.

Other GDS Versions

Six other versions of the GDS were reported in four studies (**Appendix E Table 12**). These versions included a revised 10-item version referred to as the GDS-R, and versions with one, four, five, seven, and ten questions. None of these GDS versions were used in more than two studies. In one study, the versions with fewer questions had lower sensitivity and specificity when compared to longer versions of the GDS.[171] In another study, the single-item GDS did not perform well (sensitivity 0.18 [95% CI, 0.09 to .34]), but the test accuracy of the GDS-4, GDS-10, and GDS-15 were comparable to each other in that sample.[179] The revised version (GDS-R) performed well in comparison to the GDS-15 and GDS-30, but the test performance of the GDS-R has not been replicated in other studies.

Study Characteristics of Existing Systematic Reviews

We included ten ESRs (estimated n=75,000) examining various versions of the PHQ, 2- and 3-item Whooley screening questions, CES-D, and EPDS (**Table 13**).[180-189] For the PHQ family of instruments, we included a series of IPD meta-analyses—all conducted by the same group using very similar methods. These reviews examined the accuracy of various versions of the PHQ among adults 18 years and older to screen for major depression. Participants could not be recruited from youth settings, psychiatric settings, or due to their symptoms of depression. Studies taking place in any country were eligible, although the majority took place in countries with a very high human development index. All studies were required to use either a fully structured (including the MINI) or semi-structured interview to determine the diagnosis of major depression; the interview also had to take place within 2 weeks of PHQ administration. The diagnosis of MDD or major depressive episode was determined by DSM or ICD criteria.

Results of Existing Systematic Reviews

PHQ-9

Linear Scoring

The IPD meta-analysis examining the linear scoring algorithm of the PHQ-9 included 100 studies (76 in very high HDI countries) with 44,503 participants.[188] Thirty-seven studies took place in primary care or included a general population sample, but the majority took place in inpatient or outpatient specialty care (k=63). Among the 44,503 included participants, 4,541 were diagnosed with major depression (10.2%).[190] IPD meta-analyses were conducted for PHQ cutoffs ranging from ≥5 to ≥15, grouped by the reference standard used (semi-structured, fully structured excluding the MINI, or the MINI).[190]

The standard cutoff for the PHQ-9 to identify depression is ≥10. The IPD meta-analysis confirmed a cutoff of 10 as yielding the best balance of sensitivity and specificity when compared to a semi-structured diagnostic interview (**Figure 8**). [190] For studies using a semi-structured reference standard (k=47, n=11,234) and a PHQ-9 cutoff of ≥10, sensitivity was 0.85 (95% CI, 0.79 to 0.89) and specificity was 0.85 (95% CI, 0.82 to 0.87) (**Figure 8, Appendix E Table 13**). For studies that used a fully structured reference standard excluding the MINI (k=20, n=17,167) and a PHQ-9 cutoff of ≥10, sensitivity to detect major depression was 0.64 (95% CI, 0.53 to 0.74) and specificity was 0.88 (95% CI, 0.83 to 0.92) (**Figure 8, Appendix E Table 13**). For studies that used the MINI for a reference standard (k=33, n=16,102) and a PHQ-9 cutoff of ≥10, the sensitivity to detect major depression was 0.74 (95% CI, 0.67 to 0.79) and specificity was 0.89 (95% CI, 0.86 to 0.91) (**Figure 8, Appendix E Table 13**). The AUC for all reference standards ranged from 0.84 (fully structured, excluding the MINI) to 0.90 (semi-structured) (**Appendix E Table 13**). The authors noted that older age and male sex were associated with higher specificity.[188]

A systematic review reporting the accuracy of the PHQ-9 to identify prenatal or postnatal depression was also identified. This small review (including only 4 studies from the US) reported sensitivity and specificity consistent with the results of the IPD meta-analysis of PHQ-9 among adults 18 years and older.[185] Sensitivity to identify prenatal or postnatal depression at a cutoff of ≥10 (k=3) ranged from 0.77 to 0.85 and specificity ranged from 0.62 to 0.84.[185]

Algorithm

The IPD meta-analysis examining the test accuracy of the PHQ-9 diagnostic algorithm included 54 studies (40 in very high HDI countries) with 16,688 participants.[181] Eighteen studies took place in primary care, but the majority took place in inpatient or outpatient specialty care (k=33). Two-thirds of participants (67%; n=11,130) were less than 60 years of age and 57 percent were women (n=9,512). Among the 16,688 included participants, 2,091 were diagnosed with major depression (12.5%). The diagnostic algorithm requires five or more items, each scored with 2 or more points, where at least one of these items is depressed mood or anhedonia. IPD meta-analyses were conducted for the standard algorithm scoring as well as modified scoring (only 1 point required for item 9: "Thoughts that you would be better off dead or of hurting yourself in some way"), grouped by the reference standard used (semi-structured, fully structured excluding the MINI, or the MINI).[181]

For studies using a semi-structured reference standard (k=27, n=6,331) and the original scoring, sensitivity was 0.57 (95% CI, 0.49 to 0.64) and specificity was 0.95 (95% CI, 0.94 to 0.97) (**Figure 8, Appendix E Table 13**).[181] For studies that used a fully structured reference standard excluding the MINI (k=13, n=7,577) and the original scoring, sensitivity to detect major depression was 0.35 (95% CI, 0.26 to 0.46) and specificity was 0.95 (95% CI, 0.93 to 0.97) (**Figure 8, Appendix E Table 13**). For studies that used the MINI for a reference standard (k=15, n=2,952) and the original scoring, the sensitivity to detect major depression was 0.51 (95% CI, 0.49 to 0.53) and specificity was 0.97 (95% CI, 0.96 to 0.98) (**Figure 8, Appendix E Table 13**). The modified scoring resulted in marginally higher sensitivities and similar specificities (**Appendix E Table 13**).[181]

PHQ-8

The IPD meta-analysis examining the test accuracy of the PHQ-8 included 54 studies with 16,742 participants.[186] The PHQ-8 differs from the PHQ-9 only by omission of Item 9 ("Thoughts that you would be better off dead or of hurting yourself in some way"). Forty-six percent of participants were recruited from primary care and the remaining were recruited from inpatient or outpatient specialty care. Two-thirds of participants were less than 60 years of age (n=11,144; 67%) and 57 percent were women (n=9,552). Among the 16,742 included participants, 2,097 were diagnosed with major depression (12.5%). IPD meta-analyses were conducted for PHQ-8 cutoffs ranging from ≥9 to ≥15, grouped by the reference standard used (semi-structured, fully structured excluding the MINI, or the MINI).[186]

As found for the PHQ-9, the cutoff yielding the best balance of sensitivity and specificity for the PHQ-8 was ≥10 (**Figure 8**). For studies using a semi-structured reference standard (k=27, n=6,362) and a PHQ-8 cutoff of ≥10, sensitivity was 0.86 (95% CI, 0.80 to 0.90) and specificity was 0.86 (95% CI, 0.83 to 0.89) (**Figure 8, Appendix E Table 13**).[186] For studies that used a fully structured reference standard excluding the MINI (k=13, n=7,596) and a PHQ-8 cutoff of ≥10, sensitivity to detect major depression was 0.63 (95% CI, 0.52 to 0.72) and specificity was 0.86 (95% CI, 0.81 to 0.90) (**Appendix E Table 13**). For studies that used the MINI for a reference standard (k=14, n=2,784) and a PHQ-8 cutoff of ≥10, the sensitivity to detect major depression was 0.72 (95% CI, 0.63 to 0.79) and specificity was 0.88 (95% CI, 0.84 to 0.91) (**Appendix E Table 13**). The AUC for all reference standards ranged from 0.852 (fully structured, excluding the MINI) to 0.930 (semi-structured) (**Appendix E Table 13**).[186]

PHQ-4

The IPD meta-analysis examining the test accuracy of the PHQ-4 included 75 studies (51 from very high HDI countries) with 34,698 participants.[187] The PHQ-4 is comprised of four items from the PHQ-9: depressed mood, loss of interest/pleasure, low self-esteem/guilt, and psychomotor agitation. Thirty-one studies recruited participants from the general population or primary care. The age of participants ranged from 18 to 98 years with a mean of 48 years and 59 percent were women (n=20,678). Among the 34,698 included participants, 3,392 were diagnosed with major depression (9.8%). IPD meta-analyses were conducted for PHQ-4 cutoffs ranging from ≥1 to ≥12, grouped by the reference standard used (semi-structured, fully structured excluding the MINI, or the MINI).[187]

The optimal cutoff for the PHQ-4 was identified as ≥4. For studies using a semi-structured reference standard (k=29, n=7,719) and an PHQ-4 cutoff of ≥2, sensitivity was 0.88 (95% CI, 0.81 to 0.93) and specificity was 0.79 (95% CI, 0.74 to 0.83) (**Figure 8, Appendix E Table 13**). For studies that used a fully structured reference standard excluding the MINI (k=15, n=12,109) and a PHQ-4 cutoff of ≥2, sensitivity to detect major depression was 0.68 (95% CI, 0.56 to 0.78) and specificity was 0.85 (95% CI, 0.78 to 0.90) (**Figure 8, Appendix E Table 13**). For studies that used the MINI for a reference standard (k=31, n=14,870) and a PHQ-4 cutoff of ≥2, the sensitivity to detect major depression was 0.80 (95% CI, 0.73 to 0.85) and specificity was 0.83 (95% CI, 0.80 to 0.86) (**Figure 8, Appendix E Table 13**). The AUC was not reported.[187]

PHQ-2

The IPD meta-analysis examining the test accuracy of the PHQ-2 included 100 studies (74 from very high HDI countries) with 44,318 participants.[183] The PHQ-2 is comprised of the first two items of the PHQ-9 ("Little interest or pleasure in doing things" and "Feeling down, depressed, or hopeless"). 14,450 of participants were recruited from primary care (33%), but nearly as many were recruited from inpatient or outpatient specialty care (n=14,063; 32%). Seventy-two percent of participants were less than 60 years of age (n=31,739) and 59 percent were women (n=26,034). Among the 44,318 included participants, 4,572 were diagnosed with major depression (10.3%). IPD meta-analyses were conducted for PHQ-2 cutoffs ranging from ≥1 to ≥6, grouped by the reference standard used (semi-structured, fully structured excluding the MINI, or the MINI).[183]

Optimal cutoffs for the PHQ-2 have been identified as ≥2 or ≥3, with a cutoff of ≥2 favoring sensitivity over specificity. For studies using a semi-structured reference standard (k=48, n=11,703) and an PHQ-2 cutoff of ≥2, sensitivity was 0.91 (95% CI, 0.88 to 0.94) and specificity was 0.67 (95% CI, 0.64 to 0.71) (**Figure 8, Appendix E Table 13**).[183] For studies that used a fully structured reference standard excluding the MINI (k=20, n=17,319) and a PHQ-2 cutoff of ≥2, sensitivity to detect major depression was 0.82 (95% CI, 0.75 to 0.87) and specificity was 0.71 (95% CI, 0.63 to 0.77) (**Figure 8, Appendix E Table 13**). For studies that used the MINI for a reference standard (k=32, n=15,296) and a PHQ-2 cutoff of ≥2, the sensitivity to detect major depression was 0.89 (95% CI, 0.84 to 0.92) and specificity was 0.68 (95% CI, 0.64 to 0.73) (**Figure 8, Appendix E Table 13**). At a cutoff of ≥3, sensitivity among reference standards ranged from 0.53 to 0.72 and specificity ranged from 0.85 to 0.89 (**Appendix E Table 13**). The AUC for all reference standards ranged from 0.82 (fully structured, excluding the MINI) to 0.88 (semi-structured).[183]

Sequential Administration of the PHQ-2 and PHQ-9

The systematic review and IPD meta-analysis identified for the PHQ-2 also examined the PHQ-2 in combination with the PHQ-9 (i.e., the PHQ-9 is administered if the PQH-2 is positive).[183] Forty-four studies using a semi-structured reference standard with 10,627 participants were included. Of those participants, 1,361 were diagnosed with major depression (12.8).[183] Using a cutoff of ≥2 for the PHQ-2 in combination with the PHQ-9 and a cutoff of ≥10, sensitivity to detect major depression was 0.82 (95% CI, 0.76 to 0.86) and specificity was 0.87 (95% CI, 0.84 to 0.89) (**Figure 8, Appendix Table E**).[183] Versus the PHQ-9 alone, the difference in sensitivity was -0.04 (95% CI, -0.09 to 0.01) and the difference in specificity was 0.02 (95% CI, 0.00 to 0.03).[183]

Whooley

We identified two systematic reviews examining the accuracy of the Whooley questions to screen for major depression, one including all adults[180] and one limited to prenatal women.[189] Two- and three-item Whooley questions were included.

The systematic review examining all adult populations included 10 studies with 4,618 participants.[180] Of those 4,618 participants, 602 had depression (13.0%). The diagnosis of depression had to be made using DSM or ICD criteria. Five of the studies recruited participants from primary care. Nine studies reported the percent of female participants, ranging from 3 to 100 percent of participants (35% overall).[180] The pooled sensitivity to detect major depression was 0.95 (95% CI, 0.88 to 0.97) and the pooled specificity was 0.65 (95% CI, 0.56 to 0.74) (**Figure 8**, **Appendix E Table 13**).[180] Among the five studies conducted in primary care, the pooled sensitivity was 0.96 (95% CI, 0.91 to 0.98) and the pooled specificity was 0.61 (95% CI, 0.48 to 0.73).[180]

The systematic review examining only prenatal populations included five studies with 1,402 participants (one study conducted in primary care was removed from their main analysis as an outlier and is not discussed).[189] Of those participants, 115 were diagnosed with depression (9.6%). The diagnosis of depression was made using DSM-IV and DSM-5 criteria in four studies; one study did not report the diagnostic criteria used. The pooled sensitivity of the Whooley questions to detect major depression was 0.95 (95% CI, 0.81 to 0.99) and pooled specificity was 0.60 (95% CI, 0.44 to 0.74).[189]

CES-D

We identified one systematic review examining the accuracy of the CES-D.[184] The review included 28 studies with 10,617 participants. Studies had to be conducted among participants in primary care or the general population. Eleven studies recruited only older adults and six recruited only adolescents. The diagnosis of major depression was made using DSM or ICD criteria, most commonly using the DIS, SCID, CIDI, and MINI. Of the 10,617 participants, 807 had depression (7.6%; range from individual studies, 1.8 to 37.9%).[184]

To detect major depression using the standard cutoff of ≥16, the CES-D had a pooled sensitivity of 0.87 (95% CI, 0.82 to 0.91) and a pooled specificity of 0.70 (95% CI, 0.65 to 0.75) (**Figure 8, Appendix E Table 13**).[184] Higher cutoffs (≥20, ≥22) yielded lower sensitivities and higher specificities. The AUC for the CES-D to detect major depression was 0.87. The authors noted that test accuracy was lower among younger age groups, but the age covariate was not statistically significant.[184]

EPDS

We included one recent systematic review and IPD meta-analysis examining the test accuracy of the EPDS to screen for major depression among pregnant or post-partum persons (within 12 months of giving birth), conducted by the same group who did the IPD meta-analyses for the PHQ instruments.[182] Like the others, this review was also limited to participants who were 18 years or older. Participants could not be previously identified as having possible depression or be receiving psychiatric assessment or care. A total of 58 studies with 15,557 participants were included. Of the included 58 studies, 25 were conducted with pregnant persons, 30 with postpartum persons, and three with both. Studies taking place in any country were eligible; three fifths (62%) took place in very high HDI countries (k=36). Among the 15,557 included participants, 2,069 were diagnosed with major depression (13.3%). All studies were required to

use either a fully structured (including the MINI) or semi-structured interview to determine the diagnosis of major depression; the interview also had to take place within 2 weeks of EPDS administration. IPD meta-analyses were conducted for EPDS cutoffs ranging from ≥7 to ≥15, grouped by the reference standard used (semi-structured, fully structured excluding the MINI, or the MINI).[182]

The IPD meta-analysis determined that an EPDS cutoff of ≥11 yielded the best balance of sensitivity and specificity (**Figure 8**).[182] For studies using a semi-structured reference standard (k=36, n=9,066) and an EPDS cutoff of 11, sensitivity was 0.81 (95% CI, 0.75 to 0.87) and specificity was 0.88 (95% CI, 0.85 to 0.91) (**Figure 8, Appendix E Table 13**). With the same reference standard and an EPDS cutoff of ≥12, which is a standard cutoff, sensitivity to detect major depression was 0.75 (95% CI, 0.67 to 0.81) and specificity was 0.92 (95% CI, 0.89 to 0.94) (**Appendix E Table 13**). Sensitivity and specificity estimates varied sightly with the use of the MINI and other fully structured reference standards, but generally remained in the same ranges. The AUC for all reference standards ranged from 0.890 (MINI) to 0.924 (fully structured, excluding the MINI) (**Appendix E Table 13**). The authors also noted that the test accuracy did not significantly change when EPDS administration occurred in the postpartum or pregnant period.[182]

KQ3. What Are the Harms Associated With Screening for Depression in Primary Care or Comparable Settings in Adults, Including Pregnant and Postpartum Persons?

Only one depression screening study reported on harms (**Table 8**).[159] This study, conducted in Hong Kong among post-partum patients, reported that there were no adverse events in either group. Across all depression screening studies included for KQ1, there was no pattern of effects indicating that screening might paradoxically worsen any outcomes the interventions were aiming to benefit (**Appendix E Table 14**).

KQ4. Does Treatment of Depression (Psychotherapy or Pharmacotherapy) Result in Improved Health Outcomes in Adults, Including Pregnant and Postpartum Persons?

Summary

We included 39 ESRs (reported in 41 publications) of treatment for depression, 30 addressing psychological treatment (**Table 15**)[191-220] and ten ESRs addressing pharmacologic treatment (**Table 16**).[212, 221-232] One ESR reports both psychological and pharmacotherapy treatment benefits and results are discussed under the appropriate sections.[212] Psychological treatment improved depression outcomes (**Figure 9**). This was the case in both broad analyses that included a wide range of populations and specific interventions, and in analyses of some important specific populations, including older adults, perinatal populations, and primary care patients. For example, the broadest analysis, which included any type of psychological treatment

compared to any kind of control condition, measuring the depression outcome immediately post-treatment (typically 2 to 6 months post-baseline), had a standardized mean difference (SMD) of -0.72 (95% CI, -0.78 to -0.67; k=385, N not reported, but estimated at approximately 33,000),[195] suggesting a moderate to large effect size. When limited to studies in primary care patients, the effect was smaller but clearly statistically significant (SMD, -0.42 [95% CI, -0.56 to -0.29; k=59, N not reported]). Evidence also indicated that psychological treatment for depression improved other outcomes, including anxiety symptoms, hopelessness, quality of life, social functioning, parental functioning, and mental health in offspring.

Data were limited for populations who were socially or economically disadvantaged or in specific racial or ethnic groups, however the limited evidence supported benefits of psychological treatment in these populations as well. For example, an analysis of five trials among people described as having low socioeconomic status found reduced depressive symptoms at up to 12 weeks post-baseline (SMD, -0.66 [95% CI, -0.92 - -0.41; k=5, N=424]),[212] and a separate analysis found no differences in effect size between studies limited to race or ethnic "minority" populations vs not limited to these population.[197]

For antidepressant medications, pooled effects consistently demonstrated increased rates of remission and response to treatment, and small but statistically significant reductions in depressive symptom severity in the short term (typically 8 weeks, **Figures 10–12**). For example, fluoxetine, which had the largest body of evidence with 117 studies, was associated with a small reduction in symptom severity (SMD, -0.23 [95% CI, -0.28 to -0.19]), a 46 percent increase in the odds of remission (OR, 1.46 [95% CI, 1.34 to 1.60]) and a 52 percent increase in the odds of treatment response (OR, 1.52 [95% CI, 1.40 to 1.66], number of studies and individuals included in each specific analysis was not reported, nor were I^2 values).[224] However, little information was available on the longer-term impact of antidepressants in the synthesized literature, and information was absent or extremely limited on the benefits of pharmacologic treatment in specific a priori populations of interest.

Psychological Treatment of Depression

Study Characteristics

We examined the benefits of treatment for depression using ESRs. We included 30 reviews of psychological treatment, which covered a wide range of specific intervention approaches and outcomes (**Table 15, Appendix E Table 15**).[191-220] Two of these reviews conducted meta-analyses using individual patient data,[204, 205] enabling them to examine effect modification by patient characteristics. Most other reviews conducted traditional study-level meta-analyses and provided information on effect modification by key study and intervention characteristics. Nine of the reviews utilized the Cuijpers database described in the Methods section, including up to 309 trials with control conditions in a given analysis, and approximately 33,000 participants.[194-198, 204, 205, 216]

All of the included reviews were either limited to studies of people meeting some kind of depression criteria or reported results separately for studies that were limited to those meeting depression-related criteria. Most of the included reviews were limited to studies among adults,

generally defined as 18 years and older. Some reviews focused on older adults[200, 202, 214, 217] (lowest age ranging from 50 to 65 years) and six reviews focused on perinatal patients.[203, 206, 208, 211, 213, 220] Other reviews focused on rural settings,[215] participants who were socially disadvantaged,[212] participants who were culturally and linguistically different from those for whom the intervention was originally designed,[201] or had samples that were primarily comprised of Hispanic/Latino,[193] Hispanic/Latino immigrant,[210] or Black or Hispanic/Latino[211] participants. Four ESRs focused on studies conducted among people recruited from primary care settings, in general[207, 218, 219] and older adults.[202]

Most reviews included psychological interventions without restriction to specific therapeutic approaches, however we also retained reviews that were limited to CBT-based interventions,[203, 210, 213-215, 218, 220] since this was the most widely studied therapeutic approach. Five reviews focused on electronically delivered interventions (e.g., via websites or apps),[200, 204, 205, 207, 217] and two examined telemedicine in general[192] and perinatal populations.[208] We rated all included reviews as good quality. All were published in 2015 or later, searched multiple databases with what appeared to be comprehensive search strategies; had explicit and relevant selection criteria; indicated some type of standard quality appraisal of included studies, and, if applicable, used valid meta-analytic methods.

Results

Detailed results for all outcomes are reported in **Appendix E Tables**.

Depression Symptom Severity

Most reviews explored either continuous measures of depression symptom severity, or used the studies' main outcome, which was typically a continuous measure of depression symptom severity but could also include some dichotomous outcomes that were converted to standardized effect sizes. Standardized effect sizes are shown in **Figures 9 and 13**, and **Appendix E Tables 16 and 17**. The broadest analysis, including any type of psychological treatment compared to any kind of control condition, with the main depression outcome measured immediately post-treatment, had a standardized mean difference (SMD) of -0.72 (95% CI, -0.78 to -0.67; k=385, N not reported, but estimated at approximately 34,000, **Figure 9**),[195] suggesting a moderate to large effect size. An analysis in the same review that was limited to CBT treatment reported a very similar effect size (SMD, -0.73 [95% CI, -0.80 to -0.65]; k=205, N not reported).[195] Interpersonal therapy (IPT), problem-solving therapy (PST), behavioral activation therapy (BAT), Life review, and "Third wave" cognitive therapies such as mindfulness-based approaches and Acceptance and Commitment therapy (ACT) all had SMDs of -0.60 or larger at post-treatment, with 19 to 30 studies in the analysis, as reported in the same ESR.[195]

Effects in patient populations specified a priori in our Research Plan also demonstrated greater symptom reduction with psychological interventions compared to control groups. Among perinatal patients (pregnant or postpartum), CBT was associated with an effect similar to the overall effect size at post-treatment followup(SMD of -0.69 (95% CI, -0.83 to -0.55; k=54, N=5,393, **Figure 9**).[220] An examination of the effect of internet-based CBT in postpartum patients showed a similar effect size (SMD, -0.55 [95% CI, -0.76 to -0.34]; k=6, N=635, **Figure**

9).[213] A review focused on older adults treated with CBT reported an SMD of -0.63 at post-treatment (95% CI, -0.76 to -0.49; k=52, N=2,925, **Figure 13**).[214] Psychological interventions also reduced depressive symptoms in studies of socioeconomically disadvantaged persons in the short term (SMD, -0.66 [95% CI, -0.92 to -0.41]; k=5, N=not reported), however this effect was not statistically significant at long-term followup (SMD, -0.53 [95% CI, -1.12 to 0.05]; k=4, N=not reported).[212] Effect sizes in studies among patients recruited from primary care tended to be smaller than effect sizes reported for broad analyses, not limited to studies among primary care patients. However, effect sizes among studies of primary care patients demonstrated a statistically significant benefit in most cases. For example, the SMD for any psychological treatment among primary care patients compared to any control condition was -0.42 (95% CI, -0.56 to -0.29; k=59, N not reported).[219] The effect was smaller for older adult primary care patients being treated with CBT at 26-week followup (SMD, -0.21 [95% CI, -0.40 to -0.03]; k=4, N=445)[202] but was not statistically significant when pooling the post-treatment timepoints (SMD, -0.16 [95% CI, -0.34 to 0.02]; k=4, N=274).[202] Narrative syntheses also reported generally positive effects of various psychological treatment approaches for people in rural settings and Hispanic/Latino patients, but fewer statistically significant group differences in four studies each of CBT and interpersonal therapy among Black and Hispanic/Latino perinatal patients (**Appendix E Table 18**).[211]

Depression Remission and Response

Fewer reviews reported pooled effects for depression remission[203, 204] and response to treatment[194, 204, 205] (**Table 17, Appendix E Table 19**). Analyses of remission demonstrated a two-fold or more increase in the odds of remission, among studies focused on either guided internet-based interventions or on CBT among postpartum patients. Similarly, all three analyses examining response to treatment indicated a benefit, including at followup of more than six months (OR, 1.92 [95% CI, 1.60 to 2.31]; k=55, N not reported, I^2=65) and more than one year (OR, 1.59 [95% CI, 1.14 to 2.21; k=11, N not reported, I^2=55).[194]

Other Outcomes

Reviews reported that depression treatment improved a number of other outcomes, including anxiety symptoms, hopelessness, quality of life, social functioning, days of sickness absence, parental functioning, and mental health in offspring (**Appendix E Table 20**), although some of these outcomes were sparsely reported and some effects were small. Findings for work functioning, anxiety symptom severity among postpartum patients, and suicidality did not demonstrate a statistically significant benefit, but were reported in only one,[209] two,[203] and four[194] trials, respectively (**Appendix E Table 20**).

Effect Modification and Findings in Specific Populations

We included effect modification analyses covering a wide range of study, intervention, and patient characteristics (**Figure 13, Appendix E Tables 17 and 18**). We extracted detailed results for effect modification of depression symptom severity, the most commonly reported outcome. Narrative summaries were extracted for other depression-related outcomes. Statistically significant effect modification was found for variation in study characteristics by age, the

presence of medical comorbidities, perinatal status, format, sessions per week, and some control group types. Among traditional, study-level meta-analyses, effects were smaller in studies limited to:

- General and older adults, compared to students[197]
- People with medical comorbidities[197]
- Perinatal patients[197]
- Interventions delivered in "Other/mixed" format compared to individual, group, or guided self-help formats[197]
- One or fewer sessions per week[194]
- Active control group (e.g., education group) compared with usual care or wait-list controls[214]
- Pill placebo control groups[197]
- US-based specialty mental health usual care control group, compared with specialty mental health usual care in The Netherlands[198]
- UK or Netherlands-based usual primary care, compared with US-based usual primary care[198]

In most cases, however, psychological interventions still had a statistically significant benefit even when the effect was smaller than others in the stratified analyses. Reviews with study-level meta-analyses found no effect modification related to gender composition (women only vs. women and men), race/ethnicity composition (limited to a race or ethnic "minority" group vs. not limited by race or ethnicity), recruitment setting (primary care, other medical, community, or other), usual care setting when combining studies from all countries, type of control group aside from pill placebo and active controls (e.g., wait list, usual care, no treatment), depression inclusion criteria, intervention format (individual, group, or guided self-help), and number of sessions. The individual patient data meta-analyses of internet-based interventions examined a wide range of individual-level characteristics.[204, 205] These reviews found only three characteristics that were associated with effect size: higher baseline symptom severity, older age, and being native-born to country where the study took place were all associated with larger effects for guided (but not unguided) internet-based interventions.

There was indication of publication bias in this literature. One review contacted investigators of studies in an NIH grants database that had no published results and requested the unpublished results. They then compared the pooled effect with and without the results from the unpublished studies.[199] The standardized mean difference (SMD) was reduced from -0.52 (95% CI, -0.68 to -0.37, k=20, N not reported) among published studies to -0.39 (95% CI, -0.70 to -0.08, k=26, N not reported) when the unpublished studies were included in the analysis. Additionally, a separate ESR used the Duval and Tweedie trim and fill procedure to estimate an effect adjusted for publication bias.[197] This procedure fills in "missing" studies that are hypothesized to exist but be unpublished based on the funnel plot of the data. According to this analysis, the SMD adjusted for publication bias was estimated to be -0.50 (95% CI, -0.56 to -0.44), compared with the main analysis effect of -0.71 (95% CI, -0.77 to -0.66, k=332). Thus, psychological interventions appear to reduce depression symptom severity, even taking into account the probable presence of publication bias.

Pharmacologic Treatment of Depression

Study Characteristics

We included ten ESRs of pharmacologic treatment (**Table 16, Appendix E Table 21**), covering all antidepressants commonly used in the US.[212, 221, 222, 224, 226-229, 231, 232] Our primary data source for general adult populations was an exhaustive systematic review with a network meta-analysis of antidepressants conducted by Cipriani and colleagues.[224] This review included 522 trials, covering 814 different active treatment groups (N=116,477). We focused on placebo comparisons, although this review did not report the number of studies included in each specific placebo comparison. Therefore, we reported the total number of studies included in the review for each agent in our forest plots and tables. One review each covered older,[227] perinatal,[232] primary care,[221] and socially or economically disadvantaged populations.[212] Other reviews reported outcomes not addressed by the Cipriani review, including quality of life and social functioning in older adults,[227] occupational functioning,[228] and cognitive functioning as measured by the Digit Symbol Substitution Test.[222] One review conducted individual patient-level analysis of the items of the Hamilton Depression Rating Scale to determine whether duloxetine has greater or lesser impact on specific symptoms.[229] Finally, one review reported on the effect of combined pharmacologic and psychological treatment compared to placebo.[226]

We rated seven of the included reviews as good quality.[212, 221, 222, 224, 226, 227, 232] The good quality reviews all were published in 2015 or later, searched multiple databases with what appeared to be comprehensive search strategies; had explicit and relevant selection criteria; indicated some type of standard appraisal of included studies, and, if applicable, used valid meta-analytic methods. The ESRs rated as fair were downgraded because they did not describe conducting risk of bias assessment for the studies included in their reviews.[228, 229, 231] We included these studies, however, because they either had some risk of bias safeguard (e.g., requiring double-blind design),[228] or conducted individual patient data meta-analysis which we judged to be less affected by typical risk of bias threats in component studies.[229, 231]

Most of the reviews made efforts to search for unpublished data, typically by searching conference abstracts or requesting information from the regulatory agencies or pharmaceutical companies. For example, the Cipriani review reported manual searching of trial registries and websites of drug approval agencies for unpublished studies. In addition, they contacted all of the pharmaceutical companies marketing antidepressants to ask for supplemental unpublished information about both premarketing and post-marketing studies. Finally, they also contacted study authors and drug manufacturers to supplement incomplete reports of the original papers or provide data for unpublished studies.[224]

Results

Detailed results for all outcomes are reported in **Appendix E Tables**.

Depression Outcomes

The stated primary outcome of the Cipriani review was response to treatment, typically reported as a 50 percent reduction in symptom severity measures such as the HAM-D or the MADRAS. Other depression outcomes examined were standardized mean differences of continuous symptoms severity measures and remission. In broad analyses unrestricted by population, all antidepressant agents demonstrated statistically significantly greater improvements than placebo for all three depression outcomes (**Figures 10–12; Appendix E Tables 22–24**). At 8 week followup (or the closest available), SMDs ranged from -0.17 (95% CI, -0.26 to -0.08, 17 studies included in the ESR) to -0.50 (95% CI, -0.85 to -0.15; 1 RCT, n=63), consistent with small effects for symptom severity.[224] The number of included trials ranged from one to an estimated 117, including non-placebo comparisons. The odds of remission were increased by a range of 23 percent to 252 percent and the increased odds of treatment response ranged from 37 percent to 213 percent.

The agent with the largest body of evidence was fluoxetine, with 117 trials (N not reported).[224] Fluoxetine was associated with an SMD of -0.23 (95% CI, -0.28 to -0.19) for depression symptoms severity, a 46 percent increase in the odds of remission (OR, 1.46 [95% CI, 1.34 to 1.60]) and a 52 percent increase in the odds of treatment response (OR, 1.52 [95% CI, 1.40 to 1.66], number of studies and individuals included in each specific analysis was not reported, nor were I^2 values).[224] A review addressing combination treatment (pharmacologic and psychological) also found that depression symptoms were reduced with combination treatment (SMD, -0.46 [95% CI, -0.70 to -0.21], 6 RCTs, N not reported; I^2, 17%).[226]

Among analyses limited to specific populations, findings were more variable and confidence intervals were generally wide, reflecting the small number of studies for most analyses. In a review of RCTs among primary care patients, SSRIs demonstrated a benefit for both symptom severity (SMD, -0.27 [95% CI, -0.38 to -0.16], number of studies, N, and I^2 not reported) and remission (RR, 1.33 [95% CI, 1.20 to 1.48], 7 RCTs, N=1652; I^2 not reported).[221] In a review of trials in older adults, duloxetine both had the most evidence (4 RCTs, N=1,347) and the most consistent finding of benefit across depression outcomes, while fluoxetine was the least promising.[227] In analyses among populations determined to have low socioeconomic status, one to three RCTs found greater improvements with paroxetine and with combination treatment compared to placebo.[212]

We found little information in the recent synthesized literature about longer-term effects. The review that was focused on interventions for depression among low socioeconomic status populations reported on long-term outcomes, which they defined as outcomes measured three or more months after the intervention was completed.[212] This review found one such study reporting that paroxetine was associated with lower symptom severity than placebo at 6 months' followup, 4 months after treatment had been completed (SMD, -0.39 [95% CI, -0.74 to -0.04]). This review also reported results of a meta-analysis of three studies of combination treatment. The long-term pooled effect was not statistically significant (SMD, -0.47 [95% CI, -0.97 to 0.03], I^2=85%, N=482), although the short-term finding was statistically significant for this group of three studies (SMD, -0.68 [95% CI, -0.97 to -0.40], I^2=56%, N=491). The review focused on older adults included one placebo-controlled trial of duloxetine that reported results longer than 12 weeks' followup.[227] This study reported greater symptoms reduction at long-term

followup (SMD, -0.39 [95% CI, -0.64 to -0.14]) but the remission benefit was no longer statistically significant (RR, 1.57 [95% CI, 0.95 to 2.59]).[227]

Other Outcomes

Aside from suicide-related outcomes, which are discussed under KQ5 (harms of treatment), we found very limited information on other outcomes reported in the synthesized literature of antidepressants. One review found no improvement in cognitive function as measured by the Digit Symbol Substitution Test for citalopram, duloxetine, escitalopram, nortriptyline, or sertraline, but found a small benefit for vortioxetine relative to placebo (SMD, 0.34 [95% CI, 0.18 to 0.49], 3 RCTs, I^2 and N not reported, **Appendix E Table 25**).[222] No benefits were seen for quality of life in the review focused on older adults, but one RCT of bupropion reported improved social functioning (SMD, -0.26 [95% CI, -0.06 to -0.45]).[227]

Effect Modification and Findings in Specific Populations

Detailed results are reported in **Appendix Tables 26 and 27**. The main review by Cipriani and colleagues examined some important potential effect modifiers.[224] They found larger effects in studies with earlier publication dates for several antidepressants, and also larger effects in smaller studies. They also found an association between baseline symptom severity and effect size, however this analysis was at high risk of ecological bias and is better addressed using individual patient data. Finally, they also found no association between effect size and industry sponsorship or with publication status (published vs. unpublished), however they reported having limited ability to detect the impact of these characteristics. An individual patient data meta-analysis examined effect modification for duloxetine.[229] This review found a greater reduction in suicidality with duloxetine among adults age 25 and older compared to those age 18-24, relative to placebo; duloxetine demonstrated a statistically significant benefit only in adults age 25 and older. Additionally, this review found no association between degree of improvement in depression symptoms and either baseline symptom severity or severity of side effects. A separate individual patient data meta-analysis found no association between baseline symptoms severity and effect size.[231]

KQ5. What Are the Harms of Treatment of Depression (Psychotherapy or Pharmacotherapy) in Adults, Including Pregnant and Postpartum Persons?

Summary

We included four ESRs addressing harms of psychological interventions (**Table 18**).[233-236] We included one cohort study[237] and 22 ESRs (in 29 publications) addressing harms of pharmacologic treatment for depression (**Tables 19 and 20**).[224, 227, 232, 238-255] Psychological interventions did not increase the risk of harm, as measured by deterioration of depressive symptoms.

For pharmacologic treatment, there was clear evidence that those receiving antidepressants were at a higher risk of dropout because of adverse events (**Figure 14**),[224] which likely reflect the increased risk of non-serious adverse events.[243] There was also some evidence of an increased risk of serious adverse events with SSRI use (OR, 1.39 [95% CI 1.12 to 1.72], 44 RCTs, N not reported, I^2=0%, **Figure 15**).[243] The absolute risk of serious adverse events appears to be relatively low, however, and evidence for specific serious adverse events other than suicide was very limited. There were too few suicide deaths to determine the association between antidepressant use and suicide death, but both RCT and observational evidence supported a small absolute increase in risk of suicide attempts with second generation antidepressant use among adults up to age 65 (**Figure 16**). For example, a review of FDA regulatory data indicated a 53 percent increase in the odds of a suicide attempt at post-treatment with the use of second-generation antidepressants (OR, 1.53 [1.09 to 2.15]; N= 41,861; 0.7% of antidepressants users had a suicide attempt vs 0.3% of placebo users.[256] Evidence on other outcomes was limited and generally included only observational evidence.

Psychological Treatment of Depression

Study Characteristics and Results

Four ESRs reported on adverse outcomes of psychological treatment of depression, including an estimated 63 RCTs (**Tables 18 and 21, Appendix E Table 28**).[233-236] Three of the ESRs included studies that had reported deterioration rates with any psychological treatment,[233] self-guided internet-based CBT,[236] and guided internet-based interventions.[234] Deterioration rates were either lower with psychological interventions or did not differ statistically from control groups. In the broadest analysis, which included RCTs of any type of psychological treatment that reported deterioration rates, participants in psychological interventions had a 61 percent lower likelihood of deterioration (RR, 0.39 [95% CI, 0.27 to 0.57]; 23 RCTs, N not reported; I^2, 0%). A separate review of psychological interventions among older adults reported that none of the 14 included trials reported safety data.[235]

Pharmacologic Treatment of Depression

Study Characteristics

We included 22 ESRs that addressed harms of antidepressant use (**Tables 19 and 20, Appendix E Table 29**).[224, 227, 232, 238-255] We estimated that these reviews collectively included approximately 522 RCTs and 175 observational studies. Three of these reviews covered perinatal patients,[232, 257] four focused on older adults,[227, 247, 252, 254] and the remaining included studies of adults of any age. Sixteen of the reviews were rated as good quality and six were rated fair, down-graded for lack of risk of bias assessment[238, 240, 245, 251, 257] or for only searching one database.[255] Eight of the reviews addressed the question of whether antidepressant use increased risk of suicide, primarily focused on SSRIs and other second generation agents. [237, 238, 241, 243, 247, 251, 256] We also included a large cohort study examining suicide risk that was published after the ESR we included that examined observation evidence for suicide-related outcomes (**Table 22**).[237]

Results

Detailed results are shown in **Appendix E Tables**.

Any Adverse Events, Dropout, and Serious Adverse Events

Seventeen ESRs considered non-suicidal harms of pharmacologic treatment.[224, 227, 232, 238, 239, 242-250, 252-254] A broad review examining RCTs of SSRI use compared to placebo did not report an overall estimate of the risk of any adverse event, but they examined a large number of specific non-serious events.[243] The most commonly reported events with higher rates among SSRI users were abnormal ejaculation, tremor, anorexia, nausea, somnolence, sweating, asthenia, diarrhea, constipation, insomnia, dizziness, dry mouth, libido decreased, sexual dysfunction, appetite decreased, fatigue, vomiting or upset stomach, flu syndrome, drowsiness, blurred/abnormal vision or dry eyes, nervousness, back pain, headache, dyspepsia, weight loss. These analyses included up to 78 studies per outcome (**Appendix E Table 30** for narrative summary). Neither RCT nor observational cohort evidence indicated any clear difference between the presence of the composite outcome of any adverse events for antidepressant treatment compared to placebo in older adults (**Figure 17, Appendix E Table 31**).

RCT evidence indicated no pattern of increased dropout for any reason with antidepressants, compared to placebo (**Figure 18, Appendix E Table 32**).[224] However, RCT evidence showed that whether assessed as a class (SSRI, or SNRI) or as a specific antidepressant, receiving antidepressant treatment increased the risk of dropout due to adverse events (**Figure 14, Appendix E Table 33**). Nearly every agent tested had a statistically significant increase in dropout due to adverse events among general adult populations, with ORs ranging from 1.64 (95% CI, 1.25 to 2.14, 15 RCTs, N and I^2 not reported) for Vortioxetine to 4.44 (95% CI, 3.07 to 6.50, 20 RCTs, N and I^2 not reported) for Clomipramine.[224] For older adults, SSRIs as a class increased the risk of dropping out because of adverse events nearly 3-fold (RR, 2.90 [95% CI, 1.16 to 5.06]; 3 RCTs, N=887, I^2 not reported), and SNRIs similarly increased the risk nearly two-fold (RR, 1.85 [95% CI, 1.05 to 3.27]; 3 RCTs, N=812, I^2 not reported).[252]

The association of antidepressant use with any serious adverse events was less clear (**Figure 15**, **Appendix E Table 34**). The broadest review, covering RCTs in adults reporting serious adverse events of SSRI use compared to placebo, suggested a nearly 40 percent increase in odds with antidepressant use (OR, 1.39 [95% CI 1.12 to 1.72]; k=44, N=NR, I^2 not reported).[243] Serious adverse events were relatively rare; 239/8242 SSRI participants (2.7%) had serious adverse events, compared to 106/4956 (2.1%) of placebo participants. The authors of this review rated the strength of this evidence as very low due to high risk of bias of the included studies, which they note is likely to overestimate benefits and underestimate harms. In a separate review addressing serious adverse events in older adults, only one to two studies reported serious adverse events for any specific agent (N = 122 to 607) and findings were imprecise, with wide ranging confidence intervals crossing the null. A third review examined the impact of pharmacologic interventions in perinatal patients.[232] Five RCTs and 70 observational studies were included, reporting on 27 potential serious adverse events, including maternal, birth, and infant/child harms. The authors judged the certainty of evidence to be insufficient or low in all instances, including for congenital and cardiac anomalies (graded insufficient), primarily because

of lack of control for confounding. Their findings indicated small absolute risk differences for all adverse events.

Suicide Death

Evidence for the impact of antidepressant use on suicide death was limited by the small number of events (**Figure 16, Appendix E Table 35**). The review with the most evidence involved an analysis of FDA regulatory data of 14 antidepressants, and 41 suicide deaths altogether.[256] In this review, there was a statistically non-significant 74% increase in risk of suicide with antidepressants (RR, 1.74 [95% CI, 0.78 to 3.90]; 0.12% [37/31781] died from suicide among those taking antidepressants, 0.04% [4/10080] with placebo). Other reviews included only seven suicide deaths (three with SSRI use, four with placebo)[243] and eight suicide deaths (seven of eight deaths were among those taking second generation antidepressants, one with placebo).[238] A review of cohort studies focused on older adults found only two studies examining suicide deaths.[247] One of the two cohort studies in this review was limited to people with depression, and showed a statistically non-significant effect in the direction of benefit (RR, 0.64 [95% CI, 0.38 to 1.07], n=3,325,567 prescriptions). The other cohort study in this review, among people taking SSRIs for any indication, found an increased risk of suicide death (RR, 4.87 [95% CI, 1.99 to 11.94], n=241,754 patients).

Suicide Attempts

Evidence suggested a very small increased risk of suicide attempts with antidepressant use (**Figure 16**, **Appendix E Table 35**).[238, 243, 256] For example, a review of FDA regulatory data found a 53 percent increase in the odds of a suicide attempt at post-treatment with the use of second generation antidepressants (OR, 1.53 [95% CI, 1.09 to 2.15], 206/31,781 [0.7%] of antidepressant users had a suicide attempt vs 28/10,080 [0.3%] of placebo users).[256] However, given how rarely suicide attempts occur in clinical trials, this is still based on a very small number of events. Observational evidence supported the RCT-based findings. A review of cohort and case-control studies examining the impact of second generation antidepressants found a statistically significant increase in the risk of the composite outcome of any suicide death or suicide attempt (RR, 1.29 [95% CI, 1.06 to 1.57]; k=27, N and I^2 not reported).[241] This finding held when limited to studies with low risk of bias, studies that adjusted for covariates, and studies that declared no fCOI. The increased risk was also statistically significant when limited to people with MDD, when any indication was allowed, and among studies conducted outside of North America. However, there was a statistically significant *reduction* in risk among studies conducted in North America and no association found when limited to studies with a financial COI declared. In a cohort study (N=358,351) using claims data,[237] there was no association between antidepressant dispensing and a suicide attempt leading to a medical encounter (**Table 22**). This study controlled for a wide range of patient-, physician-, and market-level variables. Effect sizes for SSRI, SNRI, and tricyclic antidepressants (TCA) dispensings had very wide confidence intervals but trended in the direction of benefit; however the association was in the direction of increased risk of a suicide attempt for people who had dispensings of two or more different kinds of antidepressants.[237]

Suicidal Ideation

One IPD MA of suicidal ideation as measured by the HAM-D suicide item found that, among adults age 25 and older, the reduction in mean suicidality ratings was larger in patients receiving SSRI from week 1 and onwards, relatively to placebo.[251] In young adults (age 18-24 years), those given an SSRI were at higher risk for worsening of suicidal ideation (in the unadjusted analysis) or emergent suicidality during the late (weeks 3-6) but not the early phase (weeks 1-2) of treatment. A separate IPD MA confirmed a lack of harms related to suicidal ideation in general and older adult populations. Fluoxetine and venlafaxine decreased suicidal thoughts and behavior for adult and geriatric patients. They determined that the protective effect was mediated by decreases in depressive symptoms with treatment.[240]

Other Serious Adverse Events

ESRs also reported on specific serious adverse events, although the evidence was limited and the data were primarily from observational studies. For falls and fractures, the available evidence was insufficient to determine whether pharmacotherapy increased the risk of serious harm (**Figure 19, Appendix E Table 36**).[246, 252] Most analyses included only one to three RCTs and few events. The largest analysis was among observational studies and found an increased risk of fracture with antidepressant use (RR, 1.67 [95% CI, 1.56 to 1.79], 23 studies, N not reported, I^2=88.4). Effect sizes were very similar in stratified analyses of studies that did and did not control for depression. These observational studies include a risk of confounding by unmeasured variables, such as indication for treatment.

For cardio- or cerebro-vascular disease, four ESRs provided data, which was primarily or entirely limited to observational studies (**Figure 20, Appendix E Table 37**).[244, 248, 249, 253] While many of the findings for stroke, intracranial hemorrhage, and venous thromboembolism showed an increased risk with antidepressant use, all reviews had a risk of confounding by indication, rendering these data insufficient to determine whether pharmacotherapy increased the risk of these serious harms. Findings were also inconclusive for mortality, dementia, and bleeding risk due to the small numbers of studies and events and most evidence being from observational studies (**Appendix E Tables 38 and 39**).

Similarly, evidence related to harms of antidepressants during pregnancy were almost entirely limited to observational evidence. An IPD meta-analysis of cohort studies found a statistically significant association between SSRI use and higher probability of preterm birth among women with depressive symptoms (OR, 1.6 [95% CI, 1.0 to 2.5]; 140/1328 (10.5) with SSRI use, 468/5652 (8.2) without SSRI, adjusted for race/ethnicity, parity, and smoking during pregnancy), but no association between either any antidepressant use or SSRI use and low birth weight, small for gestational age, or low 5-minute Apgar result (**Appendix E Table 39**). A review of 9 observational studies (n=1,287,539) examining the association between SSRI use and preeclampsia or gestational hypertension found an increased risk (OR, 1.43 [95% CI, 1.15 to 1.78]).[255] They cautioned, however, that this evidence was limited by confounding and high heterogeneity, and most studies did not account for risk factors shared between mood disorders and hypertension or for underlying risk factors shared by depression and preeclampsia. Similarly, another broader review concluded that, although many studies report on adverse events, they

could not rule out underlying disease severity as the cause of the association between exposures and adverse events.[232] The authors of this review judged the certainty of evidence to draw conclusions to be insufficient or low in all instances, including congenital and cardiac anomalies (graded insufficient), primarily because of lack of control for confounding.

Anxiety

KQ1. Do Anxiety Screening Programs in Primary Care or Comparable Settings Result in Improved Health Outcomes in Adults, Including Pregnant and Postpartum Persons?

KQ1a. Does Sending Anxiety Screening Test Results to Providers (With or Without Additional Care Management Supports) Result in Improved Health Outcomes?

Summary

We identified two RCTs (reported in 4 publications) of anxiety screening, both in general adult populations.[165, 258-260] One of these also screened for depression and several other conditions along with anxiety[165] (**Table 23**). Both trials found no reduction in anxiety symptoms or general psychological symptom severity compared with usual care at 13 to 22 weeks' followup.

Study Characteristics

Two studies examined the benefits of screening for anxiety (N=918), both conducted in the US (**Tables 23-25, Appendix F Table 1**).[165, 259] A fair-quality study published in 1994 (n=618) screened adult primary care patients and enrolled those with elevated anxiety symptoms according to the Revised Symptom Checklist-90 (SCL-90-R) whose anxiety symptoms had not been recognized by their healthcare providers.[259] Screening results for intervention participants were given to their primary care providers in the form of patient profiles showing anxiety symptoms and functional status. Primary care providers received one-on-one training in both the use of the study-provided profiles and anxiety treatment in general, and also had phone access to study physicians for questions. The average age of participants in this study was 42.6 years, 58.6 percent were women, and 80.4 percent were White. The race and ethnicity of the remaining participants was not reported. The second study (n=300, rated good quality) published in 2018 screened adult primary care patients for symptoms of anxiety, depression, sleep, pain, or fatigue and enrolled those who scored 4 or higher (out of 10) for any of these concerns.[165] Primary care clinicians were given a visual display of participants' symptom profile based on sections of the Patient-reported Outcome Measurement Information System (PROMIS). In this study, the average age of participants was 49.4 years, 71.7 percent were women, 49.3 percent were Black, and 45.0 percent were White. This study was also included above, under depression screening since it screened for both of these conditions.

Results

Both of the included studies reported that the screening programs did not improve anxiety outcomes over usual care (**Table 26**). The older study that only screened for anxiety found no differences between groups at followup in anxiety symptom levels or in any of the SF-36 subscale scores at 5 months' followup.[259] The study that screened for anxiety along with depression, pain, sleep disturbance, and fatigue reported a difference in improvement of 0.83 points on a 16-point scale at 3 months' followup (p=.47).[165] Similarly, this study also found almost identical absolute change in the General Severity Index (p=.74), a measure of mental health symptom severity. Across all outcomes reported, group differences in change ranged from -1.5 on a 16-point scale to 0.3 on a 40-point scale.

KQ2. Do Instruments to Screen for Anxiety Accurately Identify Adults, Including Pregnant and Postpartum Persons, With Anxiety in Primary Care or Comparable Settings?

Summary

We included ten primary studies (in 12 articles) that reported the test accuracy of screening for anxiety with the GAD, GAS, EPDS-anxiety subscale, or PHQ-panic disorder to detect generalized anxiety disorder, panic disorder, social anxiety disorder, or any anxiety disorder (**Table 27, Figure 21**).[29, 261-271] The most commonly studied instruments were the GAD-2 and GAD-7. To detect generalized anxiety disorder, the GAD-2 at a cutoff of ≥3 accurately identified 69 to 83 percent of adults (including pregnant women) with generalized anxiety disorder and 88 to 91 percent without it. The GAD-2 needed a lower cutoff to obtain similar test accuracy to detect any anxiety disorder, with a cutoff of ≥1 identifying a similar proportion of those with any anxiety disorder (70% to 90%), but at the cost identifying those without any anxiety disorder (55% to 64%). At a cutoff of ≥2, the GAD-2 accurately detected 50 to 91 percent of adults with a panic disorder and 63 to 74 percent of those without a panic disorder. At the same cutoff, the GAD-2 identified 85 percent of those with social anxiety disorder and 62 percent of those without. In general, the GAD-7 performed as well or better than the GAD-2.

Study Characteristics

Ten primary studies (N=6,463) were included that provided test accuracy results for anxiety screening (**Table 27**).[261-267, 269-271] Included studies primarily examined the GAD-2 and GAD-7; one study reported accuracy for the EPDS anxiety subscale, one study reported accuracy for the GAS, and one for the panic disorder module of the PHQ. Four studies were conducted in the US.[263, 265, 269, 270] The others took place in South Korea, Finland, Australia, Canada, and the UK. Sample size ranged from 50 to 1,715; four of the studies analyzed a sample of 249 participants or less.

Two studies recruited older adults (65 years or older),[263, 271] three studies recruited patients from prenatal care,[262, 266, 267] one study recruited adults who were high utilizers of primary care,[264] and

the remaining four recruited adults from primary care or the community. Mean age ranged from 29 to 75 years (k=9) (**Table 28**). Women were represented in higher proportions than men: 57 to 100 percent of participants were women. Race and ethnicity were reported in six studies. One study, conducted in South Korea, recruited only participants of South Korean ethnicity.[261] A US-based study recruited participants from an integrated community care clinic and reported that 76 percent of participants were Hispanic/Latino.[265] One study—conducted among patients using inner-city maternity services in the UK—recruited 53 percent White and 32 percent Black participants. The remaining three studies reporting race or ethnicity recruited mainly White participants (79%, 80%, and 91%).[263, 269, 270] SES was variably reported; mean years of education ranged from 14.6 to 17.3 (k=2) and those with 12 or more years of education ranged from 88 to 94 percent (k=5).

All studies used a structured or semi-structured interview within two weeks after the screener to identify generalized anxiety disorder or any anxiety disorder. The most common interviews were the MINI (k=4) and the SCID (k=4). The proportion of participants who were diagnosed with generalized anxiety disorder ranged from 1.8 percent to 16 percent, the proportion diagnosed with any anxiety disorder ranged from 3.1 percent to 32 percent, and the proportion diagnosed with panic disorder in two studies was 6.7 and 6.8 percent. The one study reporting social anxiety disorder reported a prevalence of 6.2 percent.

Results

GAD-2

Four studies reported the accuracy of the GAD-2 to detect GAD,[261, 264, 267, 270] one of which took place in the US among primary care patients (**Table 27**).[270] Despite the GAD-2 being developed to detect generalized anxiety disorder, some of these studies also reported test accuracy of the GAD-2 to detect any anxiety disorder (k=4), panic disorder (k=2), and social anxiety disorder (k=1).

Generalized Anxiety Disorder

Three studies among general adult populations reported the test accuracy of the GAD-2 to detect GAD.[261, 264, 270] At a cutoff of ≥2, the pooled sensitivity to detect GAD was 0.94 (95% CI, 0.90 to 0.98; I^2=0%) and the pooled specificity was 0.68 (95% CI, 0.64 to 0.72; I^2=94.5%). At a cutoff of ≥3, the pooled sensitivity was 0.81 (95% CI, 0.73 to 0.89; I^2=28.8%) and the pooled specificity was 0.86 (95% CI, 0.83 to 0.90; I^2=84.5%) (**Figure 22, Appendix F Table 2**).[261, 264, 270]

For the study among pregnant women (n=9,750), at a cutoff of ≥1, the sensitivity of the GAD-2 to identity GAD was 1.0 (95% CI, 0.99 to 1.0) and the specificity was 0.60 (95% CI, 0.60 to 0.61).[267] At a cutoff of ≥3, the sensitivity to detect GAD was 0.69 (95% CI, 0.64 to 0.73) and the specificity was 0.91 (95% CI, 0.90 to 0.91) (**Figure 22, Appendix F Table 2**).[267]

Any Anxiety Disorder

The same three studies among adults reported the test accuracy of the GAD-2 to detect any anxiety disorder.[261, 264, 270] At a cutoff of ≥2, the pooled sensitivity to detect any anxiety disorder was 0.76 (95% CI, 0.65 to 0.87; I^2=85.8%) and the pooled specificity was 0.73 (95% CI, 0.69 to 0.76; I^2=67.7%). At a cutoff of ≥3, the pooled sensitivity was 0.53 (95% CI, 0.39 to 0.66; I^2=86.8%) and the pooled specificity was 0.90 (95% CI, 0.88 to 0.92; I^2=48.1%) (**Figure 23, Appendix F Table 3**).[261, 264, 270]

For two studies among pregnant patients (n=528 [9,750 extrapolated] and n=954), at a cutoff of ≥1, the sensitivity of the GAD-2 to identity any anxiety disorder was 0.90 (95% CI, 0.74 to 0.97) and 0.70 (0.68, 0.73) and the specificity was 0.63 (95% CI, 0.59 to 0.66) and 0.64 (95% CI, 0.63 to 0.65).[262, 267] At a cutoff of ≥3, the sensitivity to detect any anxiety disorder was 0.30 (95% CI, 0.17 to 0.48) and 0.26 (95% CI, 0.24 to 0.29) and the specificity was 0.98 (95% CI, 0.96 to 0.98) and 0.91 (95% CI, 0.90 to 0.92)[262, 267] (**Figure 23, Appendix F Table 3**).

Panic Disorder

Two studies reported the test accuracy of the GAD-2 to identify panic disorder among adults.[264, 270] At a cutoff of ≥2, sensitivity ranged from 0.50 (95% CI, 0.19 to 0.81) among high utilizers of primary care to 0.91 (95% CI, 0.81 to 0.97) among primary care patients in the US. Specificity ranged from 0.74 (95% CI, 0.66 to 0.81) to 0.63 (95% CI, 0.60 to 0.66), respectively. At a cutoff of ≥3, sensitivity decreased (0.30 to 0.76) but specificity increased (0.81 to 0.89) (**Figure 24, Appendix F Table 4**).

Social Anxiety Disorder

One study among primary care patients in the US reported the test accuracy of the GAD-2 to detect social anxiety disorder.[270] At a cutoff of >=2, the sensitivity was 0.85 (95% CI, 0.73 to 0.93) and the specificity was 0.62 (95% CI, 0.59 to 0.65). At a cutoff of >=3, the sensitivity was lowered to 0.70 (95% CI, 0.57 to 0.81) and the specificity increased to 0.81 (95% CI, 0.78 to 0.83) (**Appendix F Table 5**).[270]

GAD-7

Six studies reported test accuracy for the GAD-7 to detect GAD, PD, SAD, or any anxiety disorder (**Table 27**).[261, 262, 264, 265, 270, 271] Four of the studies recruited adults from the community or primary care,[261, 264, 265, 270] although one was among high utilizers of primary care.[264] One study recruited community-dwelling older adults attending primary care[271] and one recruited prenatal patients.[262]

Generalized Anxiety Disorder

To detect GAD, three studies reported test accuracy for the GAD-7 at a cutoff of ≥8, ≥9, and ≥10.[261, 264, 270] At a cutoff of ≥10, the pooled sensitivity to detect GAD was 0.79 (95% CI, 0.65 to 0.94; I^2=77.3%) and pooled specificity was 0.89 (95% CI, 0.83 to 0.94; I^2=94.8%). Sensitivity

among the three studies ranged from 0.67 to 0.89, and specificity ranged from 0.82 to 0.95. At lower cutoffs (≥8, ≥9), sensitivity increased and specificity decreased (**Figure 25, Appendix F Table 2**). At higher (≥10-21) cutoffs, only one to two studies reported test accuracy data at each cutoff to detect GAD. These studies followed the same trend with higher cutoffs yielding lower sensitivity and higher specificity and lower cutoffs yielding higher sensitivity and lower specificity.

Any Anxiety Disorder

To adequately detect any anxiety disorder, lower cutoffs of the GAD-7 were necessary. At a cutoff of ≥6, pooled sensitivity of the GAD-7 to detect any anxiety disorder from four studies conducted among adults was 0.67 (95% CI, 0.48 to 0.81; I^2=90.5%; n=2,322) and pooled specificity was 0.81 (95% CI, 0.73 to 0.87; I^2=91.0%) (pooled estimate not shown in a figure).[261, 264, 265, 270] Sensitivity ranged from 0.38 to 0.85 and specificity ranged from 0.71 to 0.91 (**Figure 26, Appendix F Table 3**). At a cutoff of ≥5, the pooled sensitivity to detect any anxiety disorder among adults was 0.81 (95% CI, 0.68 to 0.95; I^2=91.4%) and the pooled specificity was 0.72 (95% CI, 0.63 to 0.81; I^2=96.1%) (pooled estimate not shown in a figure). At lower cutoffs, sensitivity increased and specificity decreased, but no more than two studies among a general adult population were represented at each lower cutoff. Similarly, at higher (≥10-21) cutoffs, only one to two studies reported test accuracy data at each cutoff to detect any anxiety disorder. These studies followed the same trend with higher cutoffs yielding lower sensitivity and higher specificity and lower cutoffs yielding higher sensitivity and lower specificity.

The one study that examined the test accuracy of the GAD-7 to detect any anxiety disorder among older adults determined the optimal cutoff was ≥5.[271] Sensitivity was 0.71 (95% CI, 0.65 to 0.76) and specificity was 0.57 (95% CI, 0.54 to 0.59) (**Figure 26**), with an AUC of 0.695 (**Appendix F Table 3**). While lower cutoffs yielded higher sensitivities (ranging from 0.80 to 0.92), the corresponding specificity was lowered to unacceptable levels (ranging from 0.25 to 0.46).[271] Similarly, higher cutoffs lowered sensitivity and increased specificity (**Appendix F Table 2**).

For the one study that recruited pregnant women, to detect any anxiety disorder, four cutoffs of the GAD-7 were reported ranging from ≥4 to ≥7.[262] Sensitivity ranged from a low of 0.43 (95% CI, 0.27 to 0.61) at a cutoff of ≥7 to a high of 0.80 (95% CI, 0.63 to 0.90) and a cutoff of ≥4. Corresponding specificity was 0.93 (95% CI, 0.91 to 0.94) and 0.71 (95% CI, 0.68 to 0.73), respectively.[262]

Panic Disorder

Two studies among adults—one among primary care patients in the US—reported the test accuracy of the GAD-7 to detect panic disorder.[264, 270] At a cutoff of ≥6 (the cutoff required to adequately detect any anxiety disorder), sensitivity to detect panic disorder ranged from 0.70 (95% CI, 0.35 to 0.93) among high utilizers of primary care to 0.88 (95% CI, 0.78 to 0.95) among primary care patients in the US and specificity ranged from 0.64 (0.60 to 0.67) to 0.79 (95% CI, 0.72 to 0.86). At a cutoff of ≥10 (the cutoff needed to detect generalized anxiety disorder), sensitivity among high utilizers of primary care was only 0.40 (95% CI, 0.12 to 0.74)

and the specificity was 0.95 (95% CI, 0.90 to 0.98). Among primary care patients in the US, a cutoff of 10 yielded a sensitivity of 0.74 (95% CI, 0.62 to 0.84) and specificity of 0.81 (95% CI, 0.78, 0.83). Both studies showed an inverse relationship between sensitivity and specificity—where lower cutoffs increased sensitivity and decreased specificity—as the cutoff was adjusted (**Figure 27, Appendix F Table 4**).[264, 270]

Social Anxiety Disorder

One study among primary care patients (n=965) in the US reported the test accuracy of the GAD-7 to detect social anxiety disorder.[270] Reported cutoffs ranged from ≥5 to ≥10. Sensitivity to detect social anxiety disorder ranged from 0.72 (95% CI, 0.59 to 0.83) at a cutoff of ≥10 to 0.88 (95% CI, 0.77 to 0.95) at a cutoff of ≥5. Specificity ranged from 0.55 (95% CI, 0.52 to 0.59) at a cutoff of ≥5 to 0.80 (95% CI, 0.77 to 0.83) at a cutoff of ≥10 (**Appendix F Table 5**).

Other Anxiety Screeners

One study reported test accuracy of the geriatric anxiety scale (GAS) to identify any anxiety disorder among 110 older adults in the US.[263] The study reported cutoffs ranging from >9 to >16 with a cutoff of >9 identified as yielding the optimal balance of sensitivity and specificity. At a cutoff of >9, sensitivity of the GAS to detect any anxiety disorder was 0.60 (95% CI, 0.31 to 0.83) and specificity was 0.75 (95% CI, 0.66 to 0.82). Sensitivity increased and specificity decreased with increasing cutoffs (**Appendix F Table 3**).[263]

Two studies[262, 266] reported the accuracy of the EPDS anxiety subscale to identify any anxiety disorder among prenatal patients; one reported the sensitivity at a single cutoff only. At a cutoff of 5, sensitivity of the EPDS anxiety subscale to detect any anxiety disorder ranged from 0.54 (95% CI, 0.38 to 0.70)[266] to 0.70 (95% CI, 0.52 to 0.83)[262]. Corresponding specificity for the single study that reported it was 0.84 (95% CI, 0.81 to 0.86).[262] At a lower cutoff of 4, sensitivity improved slightly (0.73 [95% CI, 0.56 to 0.86]) but specificity was much lower (0.71 [95% CI, 0.68 to 0.74])[262] (**Appendix F Table 3**).

One study reported the test accuracy of the panic disorder module of the PHQ to detect panic disorder among US adults in primary care.[269] If all five items of the PHQ-PD were endorsed, the sensitivity of the PHQ-PD to detect panic disorder was 0.81 (95% CI, 0.69 to 0.93) and the specificity was 0.99 (95% CI, 0.98 to 1.0) (**Appendix F Table 4**).[269]

KQ3. What Are the Harms Associated With Screening for Anxiety in Primary Care or Comparable Settings in Adults, Including Pregnant and Postpartum Persons?

Neither of the two studies of anxiety screening reported on harms, and there was no pattern of effects indicating that screening might paradoxically increase anxiety or mental health symptoms.[165, 259]

KQ4. Does Treatment of Anxiety (Psychotherapy or Pharmacotherapy) Result in Improved Health Outcomes in Adults, Including Pregnant and Postpartum Persons?

Summary

We included 26 RCTs (reported in 36 publications) among primary care patients[272-308] and 18 ESRs (not limited to primary care populations) addressing treatment for anxiety (**Tables 29–32**).[211, 215, 220, 232, 309-322] Among the 24 included RCTs of psychological interventions, 14 were in mixed populations of people with anxiety or depression, and tenwere limited to people with anxiety. Psychological interventions showed a relatively small but statistically significant reduction in anxiety symptom severity in primary care patients with anxiety (SMD, -0.41 [95% CI, -0.58 to -0.23]; 10 RCTs [n=2,075]; I^2=40.2% , **Table 33, Figure 28**), but not among mixed populations of people with anxiety or depression (SMD, -0.18 [95% CI, -0.39 to 0.03]; 12 RCTs [n=1,868]; I^2=66.7%). In the ESRs of psychological treatment, which included an estimated 144 RCTs and approximately 11,000 participants, treatment was associated with reduced anxiety symptoms; SMDs at post-treatment among broad adult populations were -0.80 and larger (e.g., among people with generalized anxiety disorder, SMD, -0.80 [95% CI, -0.93 to -0.67]; 31 RCTs, N and I^2 not reported; **Figure 29**). Psychological treatment was also associated with improved depression symptom severity and quality of life. More limited evidence suggested a benefit in older and perinatal patients as well.

There were only two RCTs of pharmacotherapy in primary care patients, addressing venlafaxine and escitalopram, and both showed a benefit. Broad ESRs (i.e., not limited to primary care patients) reported improved anxiety and other outcomes for people taking antidepressants and benzodiazepines compared to placebo. For example, among patients with generalized anxiety disorder, the SMD for change in anxiety symptom severity with SSRIs was -0.66 (95% CI, -0.90 to -0.43, 31 studies, N and I^2 not reported). For antidepressants, benefits were seen for a variety of anxiety outcomes among people with generalized anxiety disorder, social anxiety disorder, and panic disorder. Limited evidence suggested that antidepressants and benzodiazepines may improve anxiety symptoms in older adults, but evidence in perinatal patients was lacking. Improvements were also seen for depression and social functioning outcomes with pharmacotherapy.

Psychological Treatment of Anxiety

Primary Study Characteristics

We included 24 RCTs (N=5,307) that examined the benefits of psychological interventions to treat anxiety (**Table 29**),[274, 275, 277, 278, 280, 283-286, 289, 290, 292-299, 302, 304-307] including ten trials in which all participants had anxiety disorders or symptoms[278, 289, 290, 293, 294, 297, 298, 304, 305, 307] and 14 studies of participants with either anxiety or depression (i.e., some participants may not have had anxiety).[274, 275, 277, 280, 283-286, 292, 295, 296, 299, 302, 307] All interventions were either specifically targeted at anxiety, or used flexible treatment approaches that are appropriate for anxiety (e.g.,

cognitive behavioral techniques, mindfulness, problem solving approaches). Most studies (k=16) were conducted in populations of general adults.[274, 275, 277, 278, 280, 283, 284, 286, 290, 292-296, 299, 304, 305] The remaining studies were conducted in populations of older adults[285, 297, 298, 302] or perinatal populations.[274, 306, 307]

Seven of the trials were conducted in the US,[280, 286, 293, 294, 297, 298, 304] and the remaining were conducted in the UK,[277, 283, 284, 292, 305, 306] the Netherlands,[274, 295, 296] Canada,[302, 307] Sweden,[290, 299] Germany,[278, 289] Hong Kong,[285] and Spain[275]. Most trials (k=18) recruited participants from primary care clinics or other primary care relevant settings; however, two trials recruited from other clinical settings (e.g., multispecialty medical organization, university health center),[298, 302] and two trials recruited from OB-GYN and midwifery practices.[274, 306] Thirteen of the trials used screening to identify eligible participants, either entirely[274, 275, 278, 285, 295, 296, 304, 305, 307] or for a subset of participants.[286, 292, 294, 307] Only four of the trials limited to people with anxiety used screening for participant recruitment.[278, 294, 305, 306]

Seven trials were rated as good quality,[280, 290, 293, 294, 298, 304, 306] and the remaining were rated as fair quality. Common reasons for downgrading included baseline differences between treatment groups that were not statistically controlled for in analyses, excessive or differential loss to followup between groups, or inadequate methods for handling missing data.

Sociodemographic information about the included RCTs is presented in **Appendix F Table 6** and summarized in **Table 34**. Across all studies, the mean age was 45.4 years, and 74.5 percent of participants were women. Among the six trials conducted in the US and reporting on race and ethnicity,[280, 286, 293, 294, 297, 298] the majority (68.5 percent) of participants were White, 16.3 percent were Hispanic/Latino, 15.3 percent were Black, 1.5 percent were Asian American or Pacific Islander and less than one percent were Native American or Alaska Native. In studies that reported race and ethnicity data, the percentage of White participants ranged from 56.6 to 81.8 percent. None of the studies appeared to target sub-populations with significant socioeconomic challenges (e.g., low income or homelessness).

Intervention characteristics of the RCTs are summarized in **Table 35** and detailed in **Appendix F Table 7**. The most commonly utilized intervention approach was cognitive behavior therapy (CBT), with or without a support group, which was used in eighteen studies.[274, 275, 277, 278, 280, 284, 289, 290, 292-295, 297, 298, 304-307] Common components of CBT-based interventions included psychoeducation, goal-setting, cognitive restructuring, behavioral activation, self-monitoring, and problem solving. Few studies involved primary care providers in the delivery of the intervention. However, one study intervention (Coordinated Anxiety Learning and Management, or CALM) allowed participants to choose CBT, medication, or both and was delivered by nonexpert care managers who also assisted primary care clinicians in promoting medication adherence.[294] Another CBT intervention had the primary care provider delivering most or all of the intervention content, which included four individual sessions delivered in person, along with printed companion materials.[278] The most intensive CBT intervention involved up to 14 weekly 90-minute in-person manualized CBT sessions followed by 3 monthly booster sessions.[305] The least intensive CBT intervention was a 22-session app-based intervention totaling 50 minutes of therapist phone contact over an 8-week period. The intervention was delivered via a combination of web, email, text, and phone contacts.[280] Less commonly utilized intervention approaches

included problem-solving therapy (alone or with case management),[283, 285, 286, 296] mindfulness-based approaches,[299, 302] or non-directive therapy.[284] Most studies used usual care as the control condition, however some studies utilized waitlist, attention, or minimal treatment controls.

ESR Characteristics

In addition to trial evidence, we included eight ESRs that addressed psychological treatment of anxiety (**Table 31, Appendix F Table 8**).[211, 215, 220, 313-315, 317, 321] We focused on results reflecting the impact on health outcomes in general populations or in a priori populations of interest, with minimal examination of effect modification by study or intervention characteristics. Four of the reviews include studies in general adult populations,[313, 314, 317, 321] while the other reviews limited their focus to older adults,[315] general perinatal population,[323] Black and Hispanic/Latino perinatal population,[211] and rural populations.[215] All reviews included studies that addressed generalized anxiety disorder, panic disorder, and social anxiety disorder. Some reviews covered additional anxiety disorders as well, but we did not include results that were specific to disorders outside of our scope (e.g., OCD, PTSD). The largest review included 144 studies, of which 90 were specifically targeted at generalized anxiety disorder, panic disorder, and social anxiety disorder.[313]

Results (Primary and ESR Evidence)

Detailed results for all outcomes are reported in **Appendix F**.

Anxiety Outcomes

Twenty-two of the RCTs among primary care patients reported on anxiety symptoms and could be included in the meta-analysis, ranging from 8 to 30 weeks' followup.[274, 275, 277, 278, 280, 285, 286, 289, 290, 292-299, 302, 304-307] The overall pooled effect size for all twenty-two studies was statistically significant, in favor of the intervention groups (SMD, -0.29 [95% CI, -0.44 to -0.15]; 22 RCTs [n=3,943]; I^2=70.6%, **Figure 28, Table 33**). However, the pooled effect size for the twelve studies that included participants *with or without anxiety* was not statistically significant (SMD, -0.18 [95% CI, -0.39 to 0.03]; 12 RCTs [n=1,868]; I^2=66.7%), whereas the pooled effect size for the ten studies which *required participants to have anxiety* was statistically significant (SMD, -0.41 [95% CI, -0.58 to -0.23]; 10 RCTs [n=2,075]; I^2=40.2%). One RCT also reported on disorder-specific outcome measures for subgroups with specific anxiety disorder diagnoses.[294] In all cases, disorder-specific outcomes showed statistically significant improvement at 6 and 12-month followup (**Appendix F Table 9**).

One of the included RCTs offered primary care patients with panic disorder, social anxiety disorder, generalized anxiety disorder, or PTSD the choice between medication, CBT, or both in comparison to usual care.[294] First choice medications included SSRIs or SNRIs but could be augmented by another antidepressant or a benzodiazepine for non-refractory patients. While the intervention participants demonstrated greater improvements on a number of outcomes, the study did not report results separately for participants who chose medication (with or without CBT) as part of their treatment. Therefore, this study was unable to determine which specific components of the blended intervention contributed to the results.[294]

Other less commonly reported anxiety related outcomes in the RCTs included anxiety response[278, 297, 298] and anxiety remission,[278, 280] variously defined. Both studies addressing remission found greater likelihood of remission for at least one outcome among those in the intervention group, but most findings for treatment response did not demonstrate a benefit (**Appendix F Table 10**).[278, 280]

Among the ESRs, most effect sizes at the end of treatment were in the moderate to large range. For example, the broadest analyses showed clear benefits of CBT at the post-treatment assessment for generalized anxiety disorder (SMD, -0.80 [95% CI, -0.93 to -0.67]; 31 studies), social anxiety disorder (SMD, -0.88 [95% CI, -1.03 to -0.74]; 48 studies),[313] and panic disorder (SMD, -0.81 [95% CI, -1.04 to -0.59]; 42 studies, N and I^2 not reported, **Figure 29, Appendix F Table 11**). Similar benefits were seen for perinatal women. Effect sizes tended to be smaller and based on fewer studies at followup beyond the post-treatment assessment. For older adult evidence was more sparse, effect sizes had wide confidence intervals, and were frequently not statistically significant, although SMDs were all -0.20 or larger, in the direction of benefit.

Other Mental Health Outcomes, Quality of Life, and Functioning

Twenty-two of the RCTs among primary care patients reported on depression symptoms ranging from 8 to 30 weeks' followup.[274, 275, 277, 278, 280, 284-286, 290, 292-299, 302, 304-307] The overall pooled effect size for all nineteen studies was statistically significant (SMD, -0.32 [95% CI, -0.46 to -0.19]; 22 RCTs [n=3,970]; I^2=66.4%, **Figure 30, Table 33, Appendix F Table 12**), in favor of the intervention groups. The pooled effect was statistically significant both in the studies limited to people with anxiety (SMD, -0.49 [95% CI, -0.74 to -0.25]; 9 RCTs [n=1,990]; I^2=68.4%) and in mixed populations with anxiety or depression (SMD, -0.20 [95% CI, -0.34 to -0.06]; 13 RCTs [n=1,980]; I^2=39.9%; p=0.01 for the difference in effect size between studies requiring anxiety vs. those in mixed populations).

Only one RCT among primary care patients reported depression remission outcomes; that trial included people with anxiety or depression. Graham and colleagues (2020) defined treatment remission as PHQ-9 scores less than 5 or a 50 percent reduction from baseline.[280] The rate of recovery from depression was 59.4 percent in the app-based CBT intervention group and 31.0 percent in the wait list control group. The odds of recovery for depression were 3.25 (95% CI, 1.54 to 6.86) times greater for intervention participants compared with the control group.[280]

Ten RCTs among primary care patients reported on quality-of-life outcomes ranging from 8 to 30 weeks' followup.[285, 286, 290, 293-295, 297, 298, 302, 306] Few individual study findings were statistically significant, and the pooled effect sizes were small and not statistically significant for both the Mental Health Component scale of the SF-12 or SF-36 (SMD, 0.17 [95% CI, -0.03 to 0.38]; 7 RCTs [n=2,104]; I^2=54.4%) and the Physical Component Scale (SMD, 0.03 [95% CI, -0.12 to 0.18]; 5 RCTs [n=1,656]; I^2=54.4; **Figure 31**). Other health outcomes reported included global mental health symptoms,[277, 283, 284, 290] general functioning,[283, 284, 292, 294] infant outcomes (e.g., birth weight, gestational age, and Apgar scores),[274] and emergency room visits and hospitalizations,[293] and parenting adjustment.[306, 307] Very few individual findings for any of these outcomes showed statistically significant group differences (**Appendix F Tables 12–15**).

Among the included ESRs (which were not limited to primary care patients), one reported improvement in quality of life with CBT treatment for anxiety (SMD, -0.56 [95% CI, -0.80 to -0.32, 21 RCTs, N and I^2 not reported, **Figure 32, Appendix F Table 16**).[317] Another review found that depression symptoms were improved with CBT among people with generalized anxiety disorder, panic disorder, and social anxiety disorder; these findings held up even when limited to studies rated as having a low risk of bias (**Figure 32, Appendix F Table 16**).[314]

Effect Modification and Findings in Specific Populations

One of the primary RCTs by Rollman and colleagues (2018) reported subgroup analyses by age, gender, race (White vs. other race and ethnic groups), level of education, baseline GAD-7 and PHQ scores, and whether or not the participant lived alone.[293] They reported better improvements in persons age 35-59 years relative to younger and older age groups on anxiety (p=.006), depression (p=.033), and global mental health (p=.01). Participants who were not White (88% of whom were Black) reported greater improvements in depression (p=.024) than White participants, and the effect was similar but not statistically significant for anxiety (p=.08). Persons who lived alone also showed greater improvements in depression (p=.008) and anxiety (p=.01). None of the other subgroup analyses resulted in statistically significant differences, although level of education approached significance (**Appendix F Table 9**).

We stratified forest plots of anxiety symptom severity from the primary RCTs among primary care patients by population (i.e., general adult, older adult, and perinatal), whether participants were recruited via screening, and several intervention characteristics (e.g., intervention type, modality, and total contact time) to determine other factors that may modify treatment effects. We combined all studies for these analyses, both those in which all participants had anxiety and those in mixed populations. None of these factors showed as strong an association with effect size as whether the population was limited to people with anxiety compared to mixed populations (**Figure 33**). However, given the limited number of studies and the many sources of variability, we have limited confidence in whether these analyses could clarify sources of effect modification. [278, 304]

Pharmacologic Treatment of Anxiety

Primary Study Characteristics

Two RCTs (N=423) among primary care patients examined the benefits of pharmacological interventions to treat anxiety (**Tables 30 and 36**).[287, 288] Both studies were rated as good quality. Mean age across the two studies was 57.5 and 60.0 percent of the participants were women. Only one study reported race or ethnicity data and participants were 82.5 percent White.[288] The first trial (N=244; UK) assessed the efficacy of venlafaxine XL (an SNRI) in participants with generalized anxiety disorder (with and without co-morbid depression) over a 24-week period.[287] Participants were recruited from primary care settings, were over 18 years old, met DSM-IV criteria for generalized anxiety disorder, and had a score of 20 or more on the HAM-A and a score of 23 or less on the MADRS. Participants were randomized to receive 75 mg of venlafaxine or matched placebo. After 2 weeks, the dose could be doubled if initial response was poor. The second trial (N=179; US) assessed the efficacy of escitalopram (an SSRI) in older

adults with generalized anxiety disorder over a 12-week period.[288] Participants were recruited from primary care and specialty medical care (e.g., arthritis, geriatric medicine) clinics, were over 60 years old, and had a primary diagnosis of generalized anxiety disorder (defined as a score of 17 or more on the HAM-A). Participants were randomized to receive 10-20 mg of escitalopram or matched placebo.

ESR Characteristics

We also included ten ESRs of pharmacologic treatment of anxiety (**Table 32, Appendix F Table 17**), covering antidepressants, benzodiazepines, and buspirone.[232, 309-312, 316, 318-320, 322] Two reviews focused on trials in older adults[309, 316] and one focused on perinatal populations.[232] Four of the reviews were not limited to a specific anxiety disorder,[232, 309, 316, 319] two focused on generalized anxiety disorder,[312, 320] three focused on panic disorder,[310, 311, 318] and one focused on social anxiety disorder.[322] We could not determine the total number of included studies across all included reviews, but estimate that at least 227 RCTs (N approximately 40,000) were included.

All but one[319] of the included ESRs was rated good quality. The review rated as fair was downgraded because it lacked risk of bias assessment for included studies, however the focus of this review was on publication bias, and we felt risk of bias assessment was not central to this analysis. In this review, which addressed second generation antidepressants, the reviewers downloaded packets from the FDA website and submitted freedom of information requests for medications without packets. FDA information was compared with published studies to examine reporting bias, which was classified as study publication bias, outcome reporting bias, or spin. Four additional ESRs reported at least some efforts to include unpublished evidence.[232, 311, 318, 322]

Results

Detailed results for all outcomes are reported in **Appendix F**.

Primary Study Results

Anxiety and general mental health outcomes. In the trial of venlafaxine among primary care patients, participants taking venlafaxine showed greater improvement in the primary outcome of anxiety symptoms at 24 weeks followup, compared to placebo (mean difference at followup, -2.1 [95% CI, -4.2 to 0]; p = 0.05**, Appendix F Table 18**).[287] Similar findings were observed for secondary outcomes of global mental health symptom score and the Mental Health subscale of the SF-36. Group differences were not statistically significant for treatment response, remission, or depression symptoms, although all of these trended in the direction of benefit for venlafaxine.[287]

In the RCT of escitalopram, which was limited to older adults, more participants taking escitalopram met the criteria for a treatment response than those taking a placebo (OR, 1.87 [95% CI, 1.03 to 3.39]; 60% taking escitalopram compared to 45% taking a placebo, p = 0.05, **Appendix F Table 18**).[288] Treatment response was defined as a clinician rating of improved or very much improved. Participants taking escitalopram also showed greater reduction in global

mental health symptoms and anxiety symptoms, but the finding for anxiety symptoms was not statistically significant (p=.06).[288]

ESR Results

Anxiety outcomes. The continuous outcome of anxiety symptom improvement was reported on for people with generalized anxiety disorder and panic disorder in general adult populations. (**Figure 34, Appendix F Table 19**). For generalized anxiety disorder, SMDs in anxiety symptoms scores ranged from -0.23 for serotonin modulators (95% CI, -0.53 to 0.06; 8 RCTs, N=1801; I^2 not reported) to -1.84 for bupropion (95% CI, -3.05 to -0.62; 1 RCT, N=11; I^2 not applicable).[312] All but one of the seven effects were statistically significant with most in the medium to large effect size range. The effect for SSRIs was in the medium range, with the confidence intervals indicating a clearly statistically significant effect (SMD, -0.66 [95% CI, -0.90 to -0.43; 23 RCTs, N=2142; I^2 not reported).[312]

Improvements in anxiety symptoms were also reported in three reviews addressing panic disorder, with the use of antidepressants,[310] buspirone,[318] and benzodiazepines.[311] Antidepressant use was associated with improved anxiety symptoms broadly, panic symptoms, number of panic attacks, and agoraphobia symptoms.[310] SMDs ranged from -0.33 (95% CI, -0.47 to -0.20; 12 RCTs, N=2,477; I^2, 57%) for mean change in anxiety symptoms broadly to -0.69 (95% CI, -0.99 to -0.39; 13 RCTs, N=2,987; I^2, 91%) for endpoint agoraphobia scores. SSRIs showed a statistically significant benefit for all of these outcomes except for one agoraphobia outcome. TCAs showed a benefit for all but one agoraphobia and one broad anxiety symptom outcome.[310] Benzodiazepines were associated with improvements in panic symptoms and agoraphobia (range of effects: SMD, -0.35 [95% CI, -0.50 to -0.20; 13 RCTs, N=2,371; I^2, 58% to -0.92 [95% CI, -1.22 to -0.61; 7 RCTs, N=1,489, I^2, 77%).[311] However, buspirone had no impact on symptoms of agoraphobia in one small RCT (SMD, -0.01 [95% CI, -0.56 to 0.53; N=52).[318]

Two reviews reported on remission, for antidepressants[310] and benzodiazepines, both limited to studies among people with panic disorder (**Appendix F Table 20**).[311] Both types of medication demonstrated a benefit at followup of up to 28 weeks. Antidepressants demonstrated a benefit; they were associated with a 17 percent lower likelihood of failure to remit (RR, 0.83 [95% CI, 0.78 to 0.88]; 24 RCTs, N=6,164; I^2=40%; 51% taking antidepressants vs. 60% taking placebo had not remitted at post-treatment).[310] Benzodiazepines also demonstrated a benefit; they were associated with a 61 percent higher likelihood of remission (RR, 1.61 [95% CI, 1.38 to 1.88]; 15 RCTs, N=2,907; I^2=62%; 63% taking benzodiazepines vs. 40% taking placebo were in remission at post-treatment).[311] Remission was not reported for any other type of anxiety disorder.

Three reviews reported on response to treatment, for people with social anxiety disorder[322] and panic disorder (**Figure 35, Appendix F Table 21**).[310, 311] The largest body of evidence for social anxiety disorder was for SSRIs, which were associated with a 65 percent increase in the likelihood of treatment response. (RR, 1.65 [95% CI, 1.48 to 1.85]; 24 RCTs, N=4,984; I^2=50%; 54% taking SSRIs vs. 32% taking placebo met study criteria for responding to treatment).[322] For panic disorder, both antidepressants and benzodiazepines demonstrated an increased likelihood of response. Antidepressants were associated with a 28 percent reduced likelihood of failure to respond (RR, 0.72 [95% CI, 0.66 to 0.79]; 31 RCTs, N=6,500; I^2=67%; 40% taking

antidepressants, 56% taking placebo had not responded at post-treatment, not shown in the figure because it reported the inverse of all other reviews).[310] Benzodiazepines were associated with a 65 percent increased likelihood of response (RR, 1.65 [95% CI, 1.39 to 1.96]; 16 RCTs, N=2,476; I^2=67%; 65% taking benzodiazepines, 41% taking placebo were in remission at post-treatment).[311] For benzodiazepines, effect sizes were of similar magnitude and statistically significant when studies were excluded from the analyses that (a) had attrition higher than 20 percent, (b) were limited to patients with comorbidities, (c) were industry-funded, and (d) were not industry funded.[311]

Other outcomes. Reviews of RCTs among people with panic disorder and social anxiety disorder found improvements in other important outcomes (**Figure 36, Appendix F Table 22**). Reviews among people with panic disorder found statistically significant improvements in depression and social functioning with antidepressant[310] and benzodiazepine[311] use, but the effect was small and not statistically significant for quality of life with antidepressant use.[310] For example, the standardized effect size for endpoint depression symptom score was -0.41 for antidepressants after 8 to 28 weeks (95% CI, -0.57 to -0.25; 12 RCTs, N=1,794; I^2, 43%)[310] and -0.70 for benzodiazepines after 3 to 15 weeks (95% CI, -1.08 to -0.32; 8 RCTs, N=968; I^2, 78%).[311] One RCT of buspirone did not demonstrate an impact on depression for people with panic disorder.[318] For social anxiety disorder, SSRIs showed a benefit for depression, social functioning, family functioning, and work functioning, and benzodiazepines improved social and work functioning.[322]

Effect modification and findings in specific populations. In addition to effect modification findings described above for specific outcomes, one review examined publication and reporting bias for second generation antidepressants, addressing any anxiety disorder.[319] Among the 57 trials identified, the FDA interpreted 41 of the 57 trials (72%) to have positive results. However, 43 of the 45 published article conclusions (96%) were positive (P < .001). Trials that the FDA determined to be positive were five times more likely to be published compared with trials that were not positive (risk ratio, 5.20; 95% CI, 1.87 to 14.45; P < .001). The reviewers found evidence for study publication bias (P < .001), outcome reporting bias (P = .02), and spin (P = .02). The pooled effect size based on the published literature (Hedges' g, 0.38; 95% CI, 0.33 to 0.42; P < .001) was 15% higher than the effect size based on the FDA data (Hedges' g, 0.33; 95% CI, 0.29 to 0.38; P < .001), but this difference was not statistically significant (β = 0.04; 95% CI, –0.02 to 0.10; P = .18); the effect size adjusted for publication bias was statistically significant (**Appendix F Table 23**).

Two narrative systematic reviews focused on trials of older adults, and found more limited evidence that antidepressants and benzodiazepines improved anxiety symptoms among older adults (**Appendix F Table 23**).[309, 316] One review found seven placebo or waitlist-controlled RCTs, most limited to patients with generalized anxiety disorder, and reported that antidepressants were associated with reduced anxiety symptoms after 8 to 15 weeks of treatment.[309] Similarly, in three of four placebo-controlled trials limited to older adults with generalized anxiety disorder, panic disorder, or any anxiety disorder, benzodiazepines were associated with decreased anxiety during the 4- to 8-week study period (p<.05).[316] Another review that addressed pharmacologic treatment of mental health disorders in perinatal patients

found no studies of pharmacologic treatment (benzodiazepines or other anxiolytics) for anxiety among perinatal patients (**Appendix F Table 23**).[232]

KQ5. What Are the Harms of Treatment of Anxiety (Psychotherapy or Pharmacotherapy) in Adults, Including Pregnant and Postpartum Persons?

Summary

None of the RCTs or ESRs of psychological treatment reported on adverse events, but there was no pattern of effects indicating an elevated risk of harm. For the harms of pharmacologic treatment, we included three RCTs (**Table 30**)[287, 288, 324] and eight ESRs addressing medications other than antidepressants, which were addressed above under depression (**Table 32**).[232, 309-311, 316, 318, 320, 322] Evidence indicated an increase in non-serious harms as measured by a higher percent of participants experiencing any adverse events or withdrawals due to adverse events if they were taking medication (vs. placebo). Serious adverse events were rare, and data were insufficient to determine whether the risk of serious harms was increased. Case-control studies found an association between benzodiazepine use and suicide death[325] and spontaneous abortion.[326] However, the inability to fully match cases and controls on severity of mental health symptoms and other health behaviors such as substance use limited our confidence in the causal nature of these associations.

Psychological Treatment of Anxiety

None of the included RCTs or ESRs of psychological treatment of anxiety reported on harms.

Pharmacologic Treatment of Anxiety

Three primary RCTs of medication use among primary care patients reported on adverse events (n=669, **Tables 29 and 37**). These included both RCTs described under KQ4 of venlafaxine[287] and escitalopram[288] as well as an RCT of buspirone that was not included for KQ4 because it had only 4 weeks of followup.[324] All three medications were associated with statistically non-significant increases in the experience of any adverse effects (**Table 37, Appendix F Table 24**). Serious adverse effects were rare. In the trial of venlafaxine, four participants (3.3%) taking venlafaxine experienced serious adverse events compared with five (4.1%) who were taking placebo (RR, 0.79 [95% CI, 0.21 to 3.03], n=244).[287] No participants experienced serious adverse events in the RCTs of either buspirone after 4 weeks or escitalopram after 12 weeks.[288] Escitalopram had the greatest between-group difference in experiencing any adverse events (RR, 1.82 [95% CI, 0.94 to 3.51), N=177, 76% taking escitalpram vs 64% taking placebo). Among non-serious harms that were increased with escitalopram use were fatigue or somnolence ($p<.001$, 41% vs 11%) and urinary symptoms ($p=.002$, 9% vs 0%), but aches were higher in the placebo group ($p=.05$, 15% vs 6%).

Eight ESRs reported on harms or dropout for any reason (**Table 38**).[232, 309-311, 316, 318, 320, 322] Detailed results for all outcomes are shown in **Appendix F Table 25**. Dropout due to adverse events was increased with the use of antidepressants (for panic disorder),[310] SSRIs and SNRIs (for social anxiety disorder),[322] and benzodiazepines (for panic disorder)[311] (**Figure 37**). In addition, persons with panic disorder were slightly more likely to experience any adverse events when taking antidepressants, compared to placebo (RR, 1.11 [95% CI, 1.07 to 1.15); 16 RCTs, N=4,246; I^2, 0%).[310] The most common non-serious harms reported by older patients with anxiety included gastrointestinal complaints, feelings of fatigue or sedation, and sleep concerns.[309] The findings for dropout for any reason ranged from favoring pharmacotherapy to favoring placebo (**Figure 38**). Seven reviews addressing antidepressant use for any indication (including anxiety) were also included (**Table 38**), however we refer the reader to the results above under Depression (KQ5) for an examination of risks associated with antidepressant use.[244, 246, 248-250, 253, 254]

For benzodiazepine use, an extensive review of pharmacologic treatment of mental health conditions during the perinatal period concluded that the strength of evidence was low for an association with spontaneous abortion and NICU admissions (**Appendix F Table 26**).[232] The review also concluded that evidence was insufficient for preeclampsia, perinatal death, birthweight, Apgar score, and infant respiratory distress. They found no evidence on the association of benzodiazepine use with 19 other serious outcomes included in their review. Among older adults, a review of five studies of benzodiazepine treatment for anxiety found that mild adverse effects such as drowsiness, faintness, and light-headedness were more common with benzodiazepines than placebo.[316] One study in this review reported a serious adverse event (severe gastralgia) in one participant taking a placebo (at 15 days) (**Appendix F Table 26**).

Additional harms of antidepressants are reported above under the harms of depression treatment; many of those reviews included trials of antidepressant use for any indication (including anxiety disorders). Even findings in reviews specific to people with depression likely also apply to people with anxiety, given the high level of comorbidity between these two conditions.

We identified two additional case-control studies published in our search window (**Table 39**) examining the association between benzodiazepine use and spontaneous abortion (n=262,070)[326] or suicide risk (n=308);[325] outcomes that were not addressed in the ESRs. The good-quality study of spontaneous abortion was based on a cohort of 442,066 pregnancies in the Quebec Pregnancies Cohort, a cohort drawn from the Quebec Public Prescription Drug Insurance Plan.[326] The final sample included 26,789 patients with spontaneous abortions between gestation weeks 6 and 20, and 134,305 matched controls with pregnancies in the same calendar year and gestational age. Confounding variables pulled from medication dispensing databases, other medical records, and demographic databases included: antidepressant use, antipsychotic use, maternal age, welfare recipient status, urban dweller status, past 12 months' healthcare utilization (inpatient, general practice, psychiatric, other specialty), past 12 months' mental health diagnoses (mood and anxiety disorders, insomnia), folic acid exposure, and medical comorbidities (hypertension, diabetes, asthma, thyroid disorders, tobacco, alcohol or other drug dependence). This study found that benzodiazepines were associated with an 85 percent higher risk of spontaneous abortion (OR, 1.85, 95% CI, 1.61 to 2.12; 1.4% of cases had benzodiazepines dispensed vs. 0.6% of controls). They also found higher risk levels for both long- and short-acting agents, and all

specific agents, as well as a dose-response effect (all p<.05). This was a well-executed study, however they could not directly measure symptom severity or other health behaviors that may be associated with mental health symptoms such as substance use, which could be independently related to spontaneous abortion.[326]

The fair-quality case-control study of suicide risk used Sweden's national cause of death records to identify people who had died by suicide, and matched them 1-to-1 with people with mental health service use in the same timeframe by age, sex, and primary mental health diagnosis.[325] Medication exposure was determined by a prescription database. Other potential confounders controlled for included: prescriptions for antidepressants, anticonvulsants, lithium, psychostimulants, antipsychotics and sedatives; previous suicide attempt; previous psychiatric inpatient stay; previous non-psychiatric inpatient stay; age; sex; and diagnostic group (mental and behavioral disorder due to substance use, schizophrenia and related conditions, bipolar disorder, depressive disorder, anxiety disorder, disorders of adult personality and behavior, Asperger's/ADHD, and substance use). This study found that benzodiazepines were associated with an 83 percent higher odds of suicide death (OR, 1.83, 95% CI, 1.06 to 3.14; 42% of cases had benzodiazepines prescribed vs. 28% of controls). As with the other case-control study, this was a well-executed study but could not directly measure symptom severity or other health behaviors that may be associated with mental health symptoms that may be important confounders. In addition, this study relied on prescriptions rather than dispensing as the measure of benzodiazepine exposure, which is even further removed from medication actually taken.[325]

Suicide Risk

KQ1. Do Suicide Risk Screening Programs in Primary Care or Comparable Settings Result in Improved Health Outcomes in Adults, Including Pregnant and Postpartum Persons?

KQ1a. Does Sending Suicide Risk Screening Test Results to Providers (With or Without Additional Care Management Supports) Result in Improved Health Outcomes?

Summary

We found one short-term RCT (n=443) that examined screening for suicide risk, which was limited to primary care patients who had screened positive for depression (**Table 40**).[327] This trial reported no statistically significant group differences in suicidal ideation at 2 weeks' followup, and only a single suicide attempt among study participants.

Study Characteristics

One short-term RCT (n=443) was included for addressing the benefits of suicide screening, which was also included in the previous review (**Tables 40–42, Appendix G Table 1**).[327] This

trial included adult primary care patients who had screened positive for depression in general practices in the UK. Patients were randomized to suicide screening or to answer health and lifestyle questions, with the primary aim of determining whether suicide screening increased the likelihood of suicidal ideation. Participants who screened positive for suicide risk were given information about helplines and other sources of help and were encouraged to use those resources. The mean age was 48 years (range, 18 to 92 years) and 70 percent were women. Retention was 81 percent at the 2-week followup.

Results

At 2 weeks' followup, one control group participant had attempted suicide and there were no suicide attempts in the screening group (**Table 43**).[327] There were no statistically significant differences between groups in the proportion feeling that life was not worth living (28% in the screening group vs. 24% in the control group; OR, 1.23 [95% CI, 0.76 to 1.98]), wishing they were dead (23% in both groups; OR, 1.01 [95% CI, 0.61 to 1.66]), or reporting thoughts of taking their own life (15% in the screening group vs. 11% in the control group; OR, 1.36 [95% CI, 0.72 to 2.54).[327] Thus, although some outcomes trended in the direction of harm, confidence intervals were wide, making it inadvisable to draw conclusions about the short-term impact of suicide screening.

KQ2. Do Instruments to Screen for High Suicide Risk Accurately Identify Adults, Including Pregnant and Postpartum Persons, With High Suicide Risk in Primary Care or Comparable Settings?

Summary of Results

We included three studies that screened for suicidal ideation (**Table 44**).[328-330] Most screening instruments reported sensitivity and specificity above 0.80 for at least one reported cutoff (**Figure 39**). However, there was no replication of any instrument and two of the three studies included only three[328] and 12[330] individuals with suicidal ideation or at very high risk according to the reference standards. The study with the most events was limited to older adults.[329]

Study Characteristics

Three studies screening for suicidal ideation were included;[328-330] two were included in the previous review (**Table 44**).[329, 330] Each study examined a different screening test, including two versions of the Geriatric Depression Scale (GDS), three separate questions about suicide from the Symptom Driven Diagnostic System for Primary Care (SDDS-PC) (feeling suicidal, thoughts of death, wishing you were dead), and an unnamed suicide risk assessment tool. All three studies were conducted in the US. Two recruited participants from primary care and the third recruited participants from the ED for any chief complaint (i.e., not limited to patients with mental health concerns). Sample sizes ranged from 124 to 1,001. Two studies recruited adults 18 years and

older while one study recruited older adults (≥65 years) (**Table 44**). Mean age ranged from 47 to 75 years (**Table 45**). Women were represented in higher proportions than men: 52 to 63 percent of participants were women. Race and ethnicity were reported in only one study;[329] 93 percent were White. SES was reported in one study with a mean of 14 years of education.[329, 330]

Two studies used the SCID (one along with the HAM-D) to determine suicidal ideation, administered within a maximum of 4 days.[329, 330] The third used an unstructured interview from a psychiatrist administered on the day of the screening test.[328] The proportion of participants who were identified through interviews as being at risk of suicide ranged from 1.2 percent to 11 percent.

Results

GDS-15

One study reported test accuracy for the GDS-15 to identify suicidal ideation in older adults.[329] The authors determined a GDS-15 cutoff of ≥4 would maximize sensitivity and specificity, but the optimal cutoff for women alone was lower (≥3) and for men it was higher (≥5). At a GDS-15 cutoff of ≥4, sensitivity to detect suicidal ideation was 0.75 (95% CI, 0.64 to 0.84) and specificity was 0.82 (95% CI, 0.78 to 0.85) (**Appendix G Table 2**). At higher cutoffs (≥5, ≥6), sensitivity decreased and specificity increased; at lower cutoffs (≥2, ≥3) sensitivity increased and specificity decreased.[329]

GDS-SI

One study reported test accuracy for the GDS-SI. The GDS-SI is a 5-item subset of the GDS that addresses suicidal ideation (GDS items 3, 7, 11, 12, and 14).[329] The authors identified a GDS-SI cutoff of ≥1 as optimal to screen for suicidal ideation, with a sensitivity of 0.80 (95% CI, 0.69 to 0.88) and a specificity of 0.80 (95% CI, 0.77 to 0.84) (**Appendix G Table 2**). Stratified results showed at a GDS-SI cutoff of ≥1; test performance was similar between men and women. At higher cutoffs (≥2, ≥3), sensitivity decreased and specificity increased.[329]

SDDS-PC

One study (n=1,001) reported the test accuracy of three questions from the SDDS-PC to screen for suicidal ideation in primary care.[330] The sensitivity of the "feeling suicidal" symptom to identify suicidal ideation was 0.83 (95% CI, 0.62 to 1.0) and the specificity was 0.98 (95% CI, 0.97 to 0.99). The "thoughts of death" symptom resulted in a sensitivity of 1.0 (95% CI, 0.76 to 1.0) and a specificity of 0.81 (95% CI, 0.78 to 0.84). The last symptom—"wishing you were dead"—yielded a sensitivity of 0.92 (95% CI, 0.76 to 1.0) and a specificity of 0.93 (95% CI, 0.92 to 0.95) (**Appendix G Table 2**).[330]

Suicide Risk Assessment Tool

One newly identified study examined the accuracy of a new risk assessment tool.[328] The aim of the tool was to predict the risk of committing suicide within 72 hours and to replicate a

psychiatrist-recommended intervention. The risk assessment tool was replicated with a sequentially recruited ED population (n=124). Compared with an interview from a psychiatrist, the sensitivity of the tool to identify moderate or high suicide risk was 0.42 (95% CI, 0.19 to 0.68) and the specificity was 0.98 (95% CI, 0.94 to 1.0). Only 12 participants were identified as at moderate or high risk of suicide (**Appendix G Table 2**).[328]

KQ3. What Are the Harms Associated With Screening for Suicide Risk in Primary Care or Comparable Settings in Adults, Including Pregnant and Postpartum Persons?

The same short-term study (n=443) that was included for KQ1 was the only evidence included for assessing the harms of suicide screening (**Table 40**).[327] This study was designed to determine whether screening for suicide among people with symptoms of depression increased the risk of suicidal ideation. As described above under KQ1, two of three suicidal ideation items indicated a possible higher risk with screening, however the findings were inconclusive due to the lack of statistical significance and very wide confidence intervals (**Table 43**).

KQ4. Does Treatment of High Suicide Risk (Psychotherapy or Pharmacotherapy) Result in Improved Health Outcomes in Adults, Including Pregnant and Postpartum Persons?

Summary of Results

We included 23 RCTs (reported in 36 articles, N=22,632) of suicide prevention among people at increased risk of suicide (**Table 46**).[331-366] The impact of psychological interventions for suicide prevention on suicide deaths could not be determined due to the small number of events, however enough events were available to address suicide attempts. One large (n=18,882) good-quality multi-site trial conducted in US integrated care settings tested two suicide prevention interventions among adults with an elevated risk for suicide based on item 9 of the PHQ-9.[365] This study found that, compared to usual care, a care management intervention had no impact on the rate of suicide attempts (HR, 1.07 [97.5% CI, 0.84 to 1.37]; p=.52) and a low-intensity online skills training intervention was associated with an *increased* risk of suicide attempts (HR, 1.29 [97.5% CI, 1.02 to 1.64]; p=.015) Most other studies reported five or fewer suicide attempts per study group and the pooled effect was not statistically significant (OR, 0.94 [95% CI, 0.73 to 1.22]; 12 RCTs [n=14,573]; I^2=11.2%, including only the care management arm of the large trial; **Figure 40, Table 47**). Although there was a small statistically significant benefit for depression symptom severity, there was no clear improvement over usual care for suicidal ideation, self-harm, other mental outcomes, or emergency or inpatient healthcare utilization. (**Table 47**). Usual mental health care was the most common control group, and was in some cases enhanced or optimized, so most of the included studies could be considered comparative effectiveness studies. The study with the most favorable findings (n=598)used individually tailored depression care management for older adults who had screened positive for depression.[337] This study reported improvements in depression outcomes for up to one year and

suicidal ideation for up to eight months, but only five suicide attempts and one suicide death over two years. One study examined the impact of a pharmacologic intervention and found no differences between those taking placebo or 600 mg/day of lithium for up to one year in any suicide-related outcome, although medication adherence was low in this study.

Study Characteristics

23 RCTs (N=2,694) examined the benefits of interventions to prevent suicide among those at increased risk (**Table 46**),[336-338, 340, 342, 343, 345, 347-351, 353-355, 358, 359, 361-366] including one that aimed to both reduce depression and prevent suicide among older adults with a depressive disorder.[337] Two studies were restricted to older adults,[337, 359] one was limited to young adults (ages 18-25 years),[366] and none were limited to perinatal women. Many of the studies were restricted to specific populations, however, including persons meeting the criteria for borderline personality disorder,[336, 340, 342, 349, 350, 355] veterans,[338, 345, 353, 362, 364] active duty members of the US Army,[347] and college students.[348, 354, 363]

Fifteen of the trials were conducted in the US,[337, 338, 343, 345, 347-349, 353, 354, 359, 361-365] and the remaining were in Australia,[340, 366] Canada,[350] The Netherlands,[358] Denmark,[351] and the UK.[336, 342, 355] Studies used a wide range of recruitment strategies. The most common approaches were referral from medical or mental health practitioners, however three recruited through screening in primary care clinics[337, 353, 359] and one identified patients through examination of electronic medical records for PHQ-9 results, which was routinely administered at mental health visits and primary care visits for depression treatment in the participating health systems.[365] Three studies of a mobile app recruited patients from online forums, including some that focused on mental health or suicide prevention topics.[343, 351, 358] We excluded studies that recruited patients from emergency or inpatient settings who were in the midst of an acute suicidal crisis, due to limited applicability of the findings to patients who would be identified through screening in primary care settings.

Sociodemographic information about the included samples are presented in **Appendix G Table 3** and summarized in **Table 48**. Across all studies, the mean age was 33.8 years, and 66.3 percent of participants were women. Among the twelve trials conducted in the US and reporting on race or ethnicity, the percent of participants who were Black ranged from 18 to 31.9, the percent Hispanic/Latino ranged from 3.6 to 45.1, and the percent White ranged from 14.3 to 92. The highest proportions of Asian American or Pacific Islander, and Native American participants in any study were 16.1 percent and 4.8 percent, respectively. Only two trials included a sample in which less than half of participants were White, a study of veterans age 18-55[345] and one of college students[363]. Two studies appeared to be primarily comprised of people with significant socioeconomic challenges.[336, 361] One of these had a high proportion (54%) of participants who had experienced homelessness and 43 percent with an annual income below $10,000.[361] In the other study, 47.7 percent were permanently disabled and only 11.4 percent were employed.[336]

One study examined the impact of a pharmacologic intervention (lithium)[362] and the remaining examined behavioral interventions, along with usual mental health care. The most common intervention approach was dialectical behavior therapy (DBT) or programs based on DBT principles, used in seven studies (**Table 49, Appendix G Table 4**).[340, 345, 349, 350, 354, 355, 361, 365, 366]

The DBT studies were wide ranging in intensity and fidelity to original DBT approaches. They included some lower-intensity approaches such as a self-guided smartphone app,[366] a brief on-line skills development program with brief messages from an interventionist,[365] and a single 45- to 60-minute session.[361] Higher contact interventions included weekly individual and group sessions for 6 months[345] to 1 year.[349, 354, 355] DBT includes cognitive behavioral elements and directly addresses suicidal thinking and behavior. Common elements included mindfulness, emotional regulation, distress tolerance, interpersonal effectiveness, and dialectics (i.e., understanding and tolerating two simultaneous yet opposing truths, such as acceptance of a current state or skill level and a desire to improve). Three other interventions used CBT approaches: one offered up to 30 CBT counseling sessions,[342] one tested an app-based intervention[338] and the third used a CBT program to improve sleep and was limited to people with suicidal ideation and insomnia.[353] Other traditional clinical approaches included a 60-minute crisis planning meeting,[336] depression care management,[338, 365] and the Collaborative Assessment and Management of Suicidality (CAMS) approach.[347] Two other novel approaches that have not been widely used were an app-based intervention designed to increase aversion to self-injurious thoughts and behaviors through pairing of words and images,[343] and a series of expressive writing exercises.[348]

Control groups involved usual care. For most studies, this meant usual specialty mental health care (i.e., active treatment), due to the potential serious consequences of suicidal ideation. For some studies, usual care was enhanced in some way, such as by providing training to control providers, matching the amount of contact between the control and intervention groups, or limiting the control providers to those deemed to be expert clinicians in the community.

Five studies were rated as good quality[336, 338, 342, 353, 365] and the remaining were rated as fair quality. The most common reasons for downgrading studies from good to fair included attrition greater than 10 percent, lack of information about allocation concealment and randomization procedures, and questions about the baseline comparability of the groups (often secondary to small sample sizes).

Results

Detailed results for all outcomes are reported in **Appendix G**.

Suicide-Related Outcomes

Two trials reported on suicide deaths by treatment group, both at 2 years' followup.[337, 349] One study was limited to older adults and reported one death by suicide.[337] The other study was among patients with borderline personality disorder and reported no suicide deaths (**Appendix G Table 5**).[349]

Twelve trials reported suicide attempts and indicated no reduction in suicide attempts for the studied interventions.[337, 342, 345, 347, 349, 351, 354, 358, 361, 362, 364, 365] The interventions studied included DBT, CBT, CAMS, lithium, and care management. The best evidence on suicide attempts comes from a large (n=18,882) good-quality multi-site trial conducted in US integrated care settings.[365] This study tested two suicide prevention interventions among adults with an elevated risk for

suicide based on item 9 of the PHQ-9. This study found that, compared to usual care, a care management intervention had no impact on the rate of suicide attempts (HR, 1.07 [97.5% CI, 0.84 to 1.37]; *p*=.52) and an online DBT-based skills training intervention was associated with an *increased* risk of suicide attempts (HR, 1.29 [97.5% CI, 1.02 to 1.64]; *p*=.015). Estimated event rates of the primary outcome of fatal or nonfatal self harm were 3.3% for those offered care management, 3.9% for those offered skills training, and 3.1% for those receiving usual care. The skills training intervention involved minimal contact with skills coaches, who did not provide psychotherapy but sent messages through the electronic health record portal to reinforce each visit to the online program, encourage practice of specific skills, and reach out to participants without recent visits. Frequency of outreach depended on each participant's level of involvement but was at least monthly during the initial 6 months. The results for this trial held even among extensive sensitivity analyses.

Most of the remaining studies had only one to five suicide attempts in each group; only two other trials had more than ten suicide attempts in either group.[342, 349] Both of these trials were limited to people diagnosed with borderline personality disorder, and they used CBT[342] and DBT interventions.[349] Of these two, a very high-intensity DBT intervention trial was the only study to find a statistically significant reduction in suicide attempts (OR, 0.34 [95% CI, 0.14 to 0.80], n=101).[349] The intervention for this trial involved a median of 42 individual and 39 group DBT sessions. The overall pooled effect combining all twelve trials reporting this outcome (and including only the care management arm of the very large trial) was not statistically significant, with follow-up ranging from 3-months to 2-years (OR, 0.94 [95% CI, 0.73 to 1.22]; 12 RCTs [n=14,573]; I^2=11.2%, **Figure 40, Table 47**).

Twelve trials reported on change in a continuous measure of suicidal ideation severity or number of days with suicidal ideation.[338, 343, 345, 348, 349, 351, 353, 354, 361, 363, 366] The pooled analysis indicated no impact of the interventions on suicidal ideation beyond usual care (SMD, 0.14 [95% CI, -0.31 to 0.02]; I^2=54.8%, 12 RCTs, N=1,734, **Figure 41, Table 47, Appendix G Table 6**). Point estimates ranged in both directions, and only two of the individual trials reported a statistically significant improvement at any timepoint on a continuous measure of suicidal ideation.[354, 366] The trial of older adults who screened positive for depression reported a greater reduction in the percent of participants with suicidal ideation in the care management group (29.4% at baseline to 16.5% at followup) compared to usual care (20.1% to 17.1%, p=.01 for the difference between groups).[337]

Other Mental Health Outcomes, Quality of Life, and Functioning

The other mental health outcomes reported most widely included depression-related outcomes (remission, response,[337] and symptom severity,[336, 337, 342, 345, 348-350, 353, 354, 361, 366] self-harm (non-suicidal intent, or a mix of suicidal and non-suicidal intent),[336, 340, 350, 354, 355, 361] global mental health symptom severity,[336, 342, 347, 350, 355] and anxiety symptom severity (**Appendix G Tables 7 and 8**).[336, 342, 345, 361, 366]

We conducted meta-analysis for depression symptom severity scores and found that suicide prevention treatment in high-risk individuals was associated with a small, statistically significant reduction in depression symptoms (SMD, -0.22 [95% CI, -0.33 to -0.10]; 11 RCTs [n=2,177];

I^2=0%, **Figure 42, Table 47**). Three trials reported statistically significant reductions in depression symptoms, including the trial of a care management intervention among older adults who screened positive for depression; the intervention in this study also targeted depression.[337, 353, 354] This care management study found a 3.5-point greater reduction in the HAM-D for participants in the intervention group at four months post-baseline (mean difference in change from baseline [MD], -3.5 [95% CI, -4.7 to -2.3]; n=598). The effect size diminished over time, and group differences were not statistically significant at the final followup after 18 months (p=.06). This study also reported an increased likelihood of depression remission at up to 8 months' followup (OR, 2.1 [95% CI, 1.1 to 4.2]; n=487; 41.1% in the intervention group, 31.8% in the control group) and an increased likelihood of a clinically significant response at up to 1 year (OR, 2.0 [95% CI, 1.1 to 3.8]; n=405; 52.1% in the intervention group, 42.0 % in the control group reduced their HAM-D score by 50% or more).[337]

Five trials reported self-harm, all were in trials among patients with a diagnosis of borderline personality disorder or symptoms of borderline personality disorder.[336, 340, 350, 354, 355] The findings were mixed and inconclusive (**Appendix G Table 6**). Four of these trials reported the proportion of participants with episodes of self-harm but the results were inconclusive; the pooled effect had wide confidence intervals (OR, 1.21 [95% CI, 0.71 to 2.07]; 7 RCTs [n=1,009]; I^2=27.1%). On the other hand, two trials reported reductions in the number of self-harms episodes, among those with any self-harm episodes at baseline.[350, 355] One of these reported a reduced number of suicidal and self-injurious episodes at the final, 32-week followup (1.4 in the intervention group, 2.6 in the control group over the previous 12 weeks, p<.04).[350] The other trial reported a reduced number of days with self-harm in the previous 2 months (IRR, 0.91 [95% CI NR], p<.001).[355] These two studies and a third that showed a reduced proportion with self-harm were high-contact trials of DBT among patients diagnosed with borderline personality disorder.[349]

Global mental health symptom severity measures generally showed very small, statistically non-significant differences in improvement favoring the intervention groups, with most group differences being one point or less on a wide variety of scales (**Appendix G Table 8**). Similarly, anxiety symptom severity, mental health-related quality of life, global quality of life, and social function were each reported in one to four studies, with null or mixed results.

Other Health Outcomes

The very large trial found no group differences in inpatient admissions with a mental health diagnosis.[365] Two studies limited to patients with borderline personality disorder found no group differences in the proportion of patients with Accident and Emergency Department attendances or inpatient admissions (**Appendix G Table 9**).[336, 340]

Effect Modification and Findings in Specific Populations

None of the trials reported on effect modification by age, gender, race, or ethnicity, nor was there sufficient evidence to explore effect size variability by study or intervention characteristics through stratified analyses or meta-regression. The very large trial found that several demographic characteristics (sex, age distribution, race and ethnicity) and clinical characteristics (location of index visit, rates of prior mental health diagnoses) varied across levels of

intervention uptake more than expected by chance. However, these comparisons did not show a consistent relationship between baseline indicators of risk and specific levels or types of intervention participation.[365]

KQ5. What Are the Harms of Treatment of High Suicide Risk (Psychotherapy or Pharmacotherapy) in Adults, Including Pregnant and Postpartum Persons?

Two of the included RCTs of suicide prevention that we examined reported on harms.[336, 362] There were no differences between groups at followup on an instrument designed to assess the perceived level of coercion experienced by service users during hospital admission.[336] There was no pattern of effect in the studies included for KQ4 to indicate paradoxical harms of treatment. The study of lithium found a higher rate of non-serious adverse events (75.7% with lithium, 69% with placebo, p-value not reported), a slightly higher rates of serious adverse events (38.8 % with lithium, 34.1% with placebo, p-value not reported) but but no difference in withdrawals due to adverse events (1.2% with lithium, 1.5% with placebo, p-value not reported).[362]

Chapter 4. Discussion

Summary of Evidence

We addressed five key questions for each of anxiety, depression, and suicide risk, with varying levels of support for mental health screening (**Table 50**). We found both direct and indirect evidence to support screening for depression. The direct evidence is more equivocal than the indirect evidence, being a smaller body of evidence and having fewer statistically significant findings. There were some important limitations to the evidence for depression screening among older adults, where benefits were generally not seen. In addition, the lack of an unscreened control group and presence of additional program components beyond screening in many of the depression screening studies made it difficult to isolate the specific effects of screening alone in these studies. However, the indirect evidence is robust that feasible screening tools with reasonable accuracy are available, and that treatment is effective. The evidence on depression screening tools and benefits and harms of depression treatment in general and older adults were not addressed in the previous review so are newly considered. Since the USPSTF has a long-standing "B" recommendation and depression screening is becoming of the standard of care, it will grow increasingly difficult to add substantively to the evidence base of direct evidence.

We found clear evidence that there are effective treatments available to treat anxiety, particularly CBT, antidepressants, and benzodiazepines, but the direct evidence for screening for anxiety was extremely limited and did not suggest a benefit. Further, the evidence on the diagnostic accuracy of screening tools had minimal replication for anxiety disorders other than generalized anxiety disorder. Because we focused on a limited number of screening tools, there may be additional diagnostic accuracy studies available, however we believe they are unlikely to provide more robust evidence than we found.

The direct and indirect evidence on screening for suicide risk was limited, and the indirect evidence indicated that implementation of some interventions that are feasible for wide-spread use in health care systems may either have no impact on suicide attempts or may paradoxically *increase* the risk of a suicide attempt. However, the treatment evidence is predominantly compared with usual specialty mental health care, making it difficult to understand the absolute treatment effects. Unlike the previous review, the current review did not include treatment studies in persons seeking treatment in urgent or emergency settings due to their low applicability to screening in primary care settings, but with the completion of a very large implementation trial we are able to conclude that some interventions are likely ineffective or potentially harmful.

Screening for Depression

The direct evidence for the benefits of screening for depression was very similar to that in the previous review, with only two new studies added.[162, 165] Trials in general and perinatal populations demonstrate increased rates of depression remission or falling below a specified

symptom severity level after six to twelve months. The evidence in older adult populations is more limited and did not show a clear benefit. Only four studies examined screening in older adults and only one used a depression measure that was specifically designed for older adults.[157] There is ample evidence that screening instruments can identify people with MDD with reasonable accuracy, and cutoffs could be optimized for specific local settings and populations. The studies included in our review generally confirmed previously determined optimal cut-points. However, the evidence did raise some questions about the typical EPDS cutoff. While a previous meta-analysis[367] had identified a cutoff of ≥12 as optimal to identify postpartum depression using the EPDS, the IPD meta-analysis included in our review determined that an EPDS cutoff of ≥11 yielded the best balance of sensitivity and specificity (**Figure 8**).

Aside from test accuracy studies, an independent stream of evidence supports the PHQ-9 for depression screening as well, based on broad positivity rates. From 2015-2016, 7.5 percent of US adults scored ≥10 on the PHQ-9, according to National Health and Nutrition Examination Survey (NHANES) data.[368] This is only slightly higher than the estimated percent of US adults with a major depressive episode in 2015 (6.7%),[369] supporting the relative accuracy of the PHQ-9.

In contrast to our findings, the Canadian Task Force on Preventive Health Care (CTFPHC) does not recommend screening for depression, based on the lack of direct evidence on the benefits and harms of routinely screening asymptomatic adults.[370] The review that this recommendation was based on only included studies in which the screening intervention was a normal part of care and that had an unscreened comparison group. Thus, only three of the screening studies included in our review could have met their inclusion criteria and were published at the time this review was conducted, and only one[153] of these was explicitly listed as examined and excluded from their review. This study did not integrate screening into the normal care process, but instead screening was undertaken by study staff. In addition, CTFPHC stated that it "had concerns about the potential harms of screening (e.g., false positive, unnecessary treatment, labelling and stigma) and appropriate use of limited resources."

Depression Treatment

We found evidence that psychological and pharmacologic treatment for depression improve depression as well as other outcomes (e.g., quality of life), in broad patient samples as well as in studies among primary care patients. The included reviews generally reported improvements in depression symptom severity in standardized units because specific measurement tools varied across studies. Unfortunately, it is difficult to understand the clinical importance of these effect sizes, beyond Cohen's rules of thumb that 0.20, 0.50, and 0.80 could correspond to small, medium, and large effects.[371] In several of the reviews by Cuijpers and colleagues, they estimated a Number Needed to Treat (NNT) to benefit one extra person with psychological interventions compared to control conditions.[195] For the broadest finding (SMD, -0.72 [95% CI, -0.78 to -0.67]), the review authors reported a NNT of 4.0 at the end of the acute treatment phase (typically 2-6 months), assuming a control group recovery rate of 19%. NNTs ranged from 2.5 to 8.4 in this review, across sensitivity analyses and subgroup analyses for different specific types of psychological interventions, suggesting clinically important effect sizes. A separate review reported pooled response rates for psychological treatment, defined as the

proportion with 50% reduction in depression symptoms.[372] The overall response rate in psychotherapies at two months after baseline was 41% (95% CI, 38 to 43), compared with 17% (95% CI, 15 to 20) for usual care and 16% (95% CI, 14 to 18) for waitlist.[372] We also found evidence that depression treatment improves quality of life and other outcomes that may be even more important to people with depression than depressive symptoms.[373-375] While CBT was the most commonly studied specific psychological intervention and had the most support, the use of other counseling approaches was supported as well, both within our included evidence and as examined by other reviewers.[376]

While we found evidence that psychological treatment improved treatment response at one year and beyond, we found little synthesized information on the longer-term efficacy of pharmacologic treatment of depression. A network meta-analysis is underway to explore the efficacy, tolerability and acceptability of antidepressants in studies with 3-month followup or longer.[225] However, the published studies with longer-term outcomes appear to be primarily focused on whether it is beneficial to remain on antidepressants after remission, rather than on demonstrating a long-term benefit of the original course of antidepressants. Relapse prevention is outside the scope of our review; however, as an example, we did find an older review of pharmacotherapy for relapse prevention reporting that continued antidepressant use was associated with a reduction in relapse (OR = 0.35; 95% CI 0.32-0.39[377]). The review found that the effect size was not affected by patient age, drug class, depression subtype, or treatment duration. Another review that conducted a network meta-analysis examining sustained response for pharmacologic, psychological, and combination treatment, using outcomes reported at one year post-treatment initiation (or the closest available).[378] This review reported that sustained response was most likely with combination treatment, followed by psychological treatment alone. Pharmacologic treatment alone had lower rates of sustained response than either combination or psychological treatment and did not differ from usual care.

The synthesized evidence also reported effects in important patient populations. Benefits were reported for psychological treatment among studies limited to younger adults, older adults, perinatal patients, patients with or without medical comorbidities, primary care patients, and for adults who are not White (but specific race and ethnic groups were not further specified).

One important practice consideration for maximizing the effectiveness of treatment for depression is recognizing and minimizing stigma associated with depression[379] and other mental health conditions. Stigma can impede access to care via multiple mechanisms.[380] Like many Americans, some primary care clinicians carry stigmatizing attitudes toward depression, which may reduce their effectiveness in helping their patients with depression.[381] A recent survey of 71 primary care clinicians confirmed that clinicians varied in the level of stigma they felt about depression, and higher levels of stigma were found in men, medical residents, those without personal exposure to mental illness, younger clinicians, and those who reported treating depression less frequently than their counterparts. We found no studies that aimed to reduce mental health-related stigma in healthcare providers, but at the population level, anti-stigma campaigns can help reduce stigma, at least in the short term.[382]

Harms Associated With Treatment for Depression

We found that the risk of non-serious side effects is increased with the use of antidepressants, but the evidence on serious harms was more equivocal. The risk of suicide with the use of SSRIs is difficult to determine. A 2009 analysis of data from RCTs by the FDA concluded that there was an increase in the risk of suicidal behavior (suicide deaths, attempts, preparatory acts, and ideation combined) for persons younger than 25, no association for adults age 25 to 64, and a reduced risk in older adults.[383] This finding is consistent with the black-box warning on antidepressants for persons age 24 years and younger.[384] More recent evidence covered by our review, including both RCTs and observational data, suggest an increased risk of suicide attempts in adult populations younger than age 65, with a very low level of absolute risk (0.7% with second generation antidepressants vs. 0.3% with placebo in RCTs).[256] The review that reported this finding conducted a number of analyses using different pooling methods. We selected the effect we believed to be most consistent with the AHRQ Evidence-based Practice Center (EPC) program guidance, which was the Peto OR. Other methods reported in the review and supported by the EPC program guidance included a fixed effect Mantel-Haenszel model and Bayesian approaches, and these models also demonstrated statistically significant increases in risk. However, this analysis was not stratified to determine effects in adults younger than 25 compared with those age 25 and older. We did find weak evidence that suicidal ideation is more likely to increase with antidepressant use in adults ages 18-24 than for those age 25 years and older, in whom suicidal ideation typically declined.

Suicide deaths in treatment studies are very rare, and analyses were typically underpowered. Based on an analysis of FDA regulatory data, the increased risk of suicide death was not statistically significant in placebo-controlled trials, but was based on only 41 deaths altogether, 37 of which occurred among participants taking SSRIs and other second-generation antidepressants. Both RCTs and observational studies found increases in the risk of suicide attempts among those taking second generation antidepressants. In RCTs, followup with typically only 8 weeks and was limited to people taking SSRIs for MDD. In observational studies, the increase in risk for the composite outcome suicide attempts or death was confirmed when antidepressants were used for depression as well as other indications. Interestingly, observational studies indicated no harmful association among 21 studies conducted in North America, but there was a harmful association among 36 studies conducted in Europe. Further, the harmful effect was present only among the 33 studies *without* a financial conflict of interest declared. These findings suggest a risk of publication or reporting bias among observational studies as we identified among RCTs. Observational studies are inherently limited, however, due to confounding by indication, disease severity, and other variables that are difficult or impossible to control for.

We found no recent ESRs that examined suicide outcomes of non-pharmacologic treatment of depression, and we have found no other evidence indicating the psychological treatment of depression may be associated with an increased risk of suicidality or any other harms.

Screening for Anxiety

The direct evidence for anxiety screening was extremely limited and did not suggest a benefit. In our examination of the accuracy of anxiety screening tools, we made an a priori decision to focus on a limited number of tools we believed to be most widely used, but only one of them was designed to detect panic disorder and none were designed for social anxiety disorder, specifically. The anxiety screening studies (KQ1) used a single item screener and the 90-item Symptom Checklist-90 to screen for anxiety, neither of which were included in our review for diagnostic accuracy. Two of our included anxiety treatment studies used the five-item Overall Anxiety Severity and Impairment Scale (OASIS) as a screening tool for identifying potential participants. We did not find any diagnostic accuracy studies for this tool among general (non-clinical) adult samples; however, a US-based study among primary care patients whose clinician suspected that they had anxiety reported a sensitivity of 0.89 and specificity of 0.71 at a cut-point of 8 for the OASIS, compared to a structured interview using the MINI. Because there are many disorders that manifest with anxiety symptoms (e.g., PTSD, OCD, ADHD, depression, autism-spectrum disorders), sensitivity may be the more important than specificity when evaluating these tools. If tools identify patients with other conditions that need treatment as well as anxiety disorders, there could still be a net value of screening.

Anxiety Treatment

We found broad evidence that treatment for anxiety disorders is effective, including samples with social anxiety disorder, panic disorder, generalized anxiety disorder and mixed samples with any of these anxiety disorders. We also found evidence to support a benefit of psychological treatment among primary care patients, albeit with a smaller effect size than that for anxiety treatment overall. The clinical importance of the effect among primary care patients is difficult to determine but may be judged by the findings in studies with effects close to the size of the overall pooled effect. In one study with a standardized symptom change score very close to the overall pooled effect, 57 percent of the intervention group participants had reduced their anxiety symptom score by 50 percent or more, compared to 37 percent in the usual care group, which suggests a clinically important effect.[294] The other study with an effect very close to the pooled effect reported a difference in change between groups on the GAD-SS of 0.3 points, which was not statistically significant. However, the intervention group on average met this study's stated criteria for clinically important change of two or more points, with a mean (SD) change of -2.8 (3.8) points from baseline to followup; the control group did not meet this criterion (mean [SD] change, -1.6 [4.2]).[298]

Among studies in mixed populations of people with depression or anxiety, several studies used the Hospital Anxiety and Depression Scale (HADS) as the outcome measure, and differences between groups in absolute change scores were universally smaller than estimates of minimal clinically important difference[385] of 1.7. However, we excluded the HADS in our examination of diagnostic accuracy because another review concluded that the underlying structure of the HADS is inconsistent across samples and highly dependent on the statistical methods used to establish that structure.[386] The reviewers concluded that it should not be used to measure depression and anxiety specifically, but should only be used as a measure of general distress.

Commentators have suggested discontinuing the use of the HADS because it is not a dependable tool for assessing the absolute or relative levels of anxiety or depression.[387]

Most of the primary studies were conducted outside the US. Most participants included were White, and most studies targeted general adult (versus older adult or perinatal) populations. Most studies utilized CBT-based interventions and few studies directly involved primary care providers in the delivery of treatment. Few studies reported effect modification in specific populations of interest, but one US-based RCT reported that treatment was more effective in persons 35-59 years of age (relative to younger or older age groups), in White individuals (relative to persons of other racial or ethnic groups), and persons who live alone. A separate review found a standardized mean difference of -0.39 (95% CI, -0.63 to -0.15) for primary care patients with depression or anxiety treated with CBT.[218] This effect size is slightly larger than our findings of -0.21 (95% CI, -0.35 to -0.06) among people with anxiety or depression, and -0.31 [95% CI, -0.44 to -0.19] when limited to individuals with anxiety. Their analysis included some studies excluded from our review because they were limited to people with certain medical conditions or because they received poor-quality ratings.

Potential pharmacological treatments for anxiety include antidepressants (particularly SSRIs and SNRIs), antihistamines (such as hydroxyzine), beta-blockers (such as propranolol), and anti-convulsant medications (such as gabapentin).[388] Benzodiazepines, such as alprazolam or clonazepam, are often prescribed for acute anxiety or panic attacks. Buspirone is often used as an alternative to benzodiazepines because it is associated with a lower risk of dependence. Despite the variety of treatment options, we found only two RCTs of pharmacotherapy in primary care patient populations; both studies reported benefits of treatment with antidepressants (specifically venlafaxine and escitalopram) for up to 24 weeks. Broad ESR evidence (not limited to primary care populations) also suggested improvements in anxiety and other outcomes (such as depression and social functioning) for general adults or older adults taking antidepressants or benzodiazepines for one to three months. Additional research is needed to address the benefit of pharmacological treatment for anxiety in perinatal populations.

Harms Associated With Treatment for Anxiety

Antidepressants are widely used for the treatment of anxiety, and many of the reviews we included examined the risk of harm for any indication (including anxiety). Thus, many of the findings on antidepressant use for depression also apply to antidepressant use for anxiety. Beyond antidepressants, we found very limited evidence on risk of serious harm with pharmacologic treatment for anxiety, in both primary studies and existing systematic reviews. One included study examined the risk of suicide with benzodiazepine use as a treatment for anxiety; this was a relatively small case-control study that included information on 154 suicide deaths. We also found a systematic review that examined studies reporting the association between benzodiazepines and suicide, although it did not meet our quality criteria because it searched only one database and did not examine risk of bias (which we felt was particularly important when synthesizing observational studies).[389] However, it did identify 17 studies, most of which found an association between benzodiazepine use and suicide, covering a range of study populations. Although we did not find synthesized evidence on the risk of addiction or misuse of benzodiazepines in our search window, the FDA issued a warning in 2020:

"…even when taken at recommended dosages, [benzodiazepine] use can lead to misuse, abuse, and addiction. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioid pain relievers, alcohol, or illicit drugs. Physical dependence can occur when benzodiazepines are taken steadily for several days to weeks, even as prescribed. Stopping them abruptly or reducing the dosage too quickly can result in withdrawal reactions, including seizures, which can be life-threatening."[390]

In addition, the FDA has issued a warning on the dangers of combined use of benzodiazepines with opioid medicines (including prescription pain and cough medications that contain opioids) and other central nervous system depressants.[391] This combination can result in slowed or difficult breathing and death. While the absolute number of overdose deaths associated with prescription benzodiazepine use is low, it increased by 21% between 2019 and 2020, from 921 to 1,122 per 100,000; 92.7% of these overdoses also involved opioids.[392] Thus, while effective, multiple streams of evidence suggested a need for caution and close monitoring for benzodiazepines. Benzodiazepines are controlled substances with the potential for abuse, and are known to be misused, particularly among people with a history of alcohol and substance misuse.[393] They can also negatively affect cognition, even after discontinuation of use, although the clinical significance of the cognitive effects are unclear.[394] Among older adults, benzodiazepines are association with harmful drug interactions, psychomotor slowing, cognitive dysfunction, an increased risk of falls at attendant hip and femur fractures, and an increased risk of motor vehicle crashes.[393] We did not find any evidence on risks of treatment using anxiolytic medications other than benzodiazepines.

Screening for Suicide Risk

Suicide prevention efforts have the potential to save many American lives, and according to the CDC, success in preventing suicide is most likely if addressed at multiple levels and in multiple sectors.[7] While there is surely an important role for healthcare settings, we found only one trial reporting direct evidence on suicide risk screening, in primary care patients who had screened positive for depression. The findings were inconclusive. We scoped the review to include evidence on screening in broad populations (not only those who screen positive for depression), but we found no such evidence. In addition, we found minimal evidence on the test performance of suicide risk screening instruments; no instrument was addressed in more than one study.

Studies without control groups (and therefore not included in our review) have indicated that asking adults about suicidality in mental health settings does not increase suicidality.[356, 395, 396] Similarly, a randomized trial among adults with borderline personality disorder comparing frequent and repeated mental health assessment (five times per day initially, then daily, then weekly) with or without items assessing suicidal ideation, found no increase in suicidal thoughts or behaviors with suicide-related screening compared with mental health screening without suicide-related items.[397] Some healthcare systems have implemented suicide risk screening in primary care settings, without reports of harms. These include the VA system, which recommends using the PHQ-9,[398] a depression screener that includes a suicide-related item, and the Chickasaw Nation Departments of Health and Family Services,[399] which recommends administering the full PHQ-9 to those who screen positive on the PHQ-2. Given the risks associated with suicidal ideation and significant wait times between referral and receipt of

appropriate mental health care that may occur in many settings, developing a safety plan for suicidal individuals while awaiting care must be considered.

Qualitative patient interviews among people who screened positive for depression on the PHQ-2 in primary care settings and subsequently completed the PHQ-9 indicated that being asked about suicidal thoughts felt appropriate and valuable, given the context of their positive depression screen.[400] One theme that emerged, however, was difficulty answering the PHQ-9 item about suicide ("Thoughts that you would be better off dead, or thoughts of hurting yourself in some way"). For example, some felt that while they thought about suicide or wishing they were dead, they felt strongly that they would never attempt suicide. Another theme that emerged was that disclosing their thoughts of suicide or wishing to be dead involved weighing the hope for help against fears of negative consequences, such as fear of loss of autonomy, stigma, judgment, and feelings of shame and vulnerability. Another theme reinforced the importance of a trusting relationship with the provider and the value of the provider's willingness to listen without judgement.

However, there may be other potential harms of screening for suicide risk in primary care settings. For example, there are documented cases in which health care associated with suicide attempts has been denied coverage[401, 402] by medical insurance, and having a positive suicide risk screener may increase the risk that some types of injuries could be interpreted as suicide attempts. Similarly, life insurance payouts could potentially be affected by findings of increased suicide risk in medical records, since most policies do not pay out for suicide deaths in the first two years of coverage.[403, 404] Thus, a screening result in the medical record indicating an elevated risk of suicide could result in serious financial implications for people who struggle with mental health issues and their families. In addition, clinicians who fail to adequately intervene to prevent suicide in patients screening positive for suicidal ideation may be vulnerable to malpractice suits if a patient dies by suicide who screened positive for suicidal ideation,[405] despite the fact that suicidal ideation has very limited accuracy in predicting suicide attempts and death in primary care settings. These types of structural barriers for patients and clinicians are examples of why multi-level and multi-sector efforts are needed to make suicide prevention programs as effective as possible.

Predicting Future Suicide Attempts (Contextual Question 4)

For the accuracy of suicide risk screening tools, our review focused on tools to determine the presence of *current* suicidal ideation, but we did not address the ability of these tools to predict *future* suicide attempts and deaths. The odds of a future suicide attempt and suicide death approximately double in the presence of suicidal ideation.[406] One study found that mental health patients with nearly daily suicidal ideation according to the PHQ-9 suicidality item were five to eight times more likely to attempt suicide and three to eleven times more likely to die by suicide within 30 days than those without suicidal ideation.[407] Similarly, the same group of researchers found that the 13% of patients in a large managed care system who reported thoughts of death or self-harm "more than half the days" or "nearly every day" according to the suicidality item of the PHQ-9 accounted for 53% of suicide attempts and 54% of suicide deaths over the 5 years of observation.[408] In this health system, clinicians in all settings were encouraged to administer the PHQ-9 to patients with depression for symptom monitoring, so this was largely a sample of

patients known to have depression. The relationships between suicide thoughts and attempts and deaths were similar across age groups.

However, given the very rare nature of suicide (14/100,000 persons annually), the absolute predictive value of suicidal ideation to predict suicide attempts and deaths is very low, especially among non-psychiatric patients. Non-psychiatric patients with suicidal ideation have an estimated 0.23% absolute risk of suicide over the next year.[409] Studies indicate that approximately 70% of people who die by suicide will have denied suicidal ideation at their last clinical contact.[82, 410] For example, 67% of decedents in a study of 157 people who had died by suicide had denied suicidal ideation at last contact, and fifty percent of those who had been asked and denied suicidal ideation died within 2 days of that encounter.[82] Thus, assessing for suicidal ideation is only part of the risk assessment process. A comprehensive risk assessment is needed to estimate future suicide risk, including access to means of suicide and factors such as depression, anxiety, substance use, chronic and current stressors, sleep, prior history of self-harm, and physical health.

We did not examine studies of suicide risk prediction models, which use electronic algorithms based on information in medical and administrative databases to estimate suicide risk. These approaches have the potential benefit of broad reach since they could be implemented across an entire health system at relatively low cost. However, a review of modern-generation risk prediction models, including those that use machine learning algorithms, concluded that these tools are also likely inadequate for widespread use.[411] This review found that PPVs for suicide deaths ranged from <0.1% to 19%, and ranged from 0% to 78% in predicting suicide attempts.[411] Risk prediction appears to be more successful in the context of specialty mental health, where one study found that people with risk scores in the top 5% accounted for 43% of subsequent suicide attempts and 48% of suicide deaths.[412] However, PPV is still quite low even among mental health patients. A systematic review of the PPV of tools for predicting suicide deaths or self-harm in cohorts of psychiatric patients found that an estimated 5.5% of patients stratified as high risk will die by suicide, compared with 0.9% of lower-risk patients, over an average followup of 63 months.[413] In this review, an estimated 44 percent of suicide decedents would have been classified as low risk.[413]

Unfortunately, there may also be a risk of promoting health inequities with the use of some electronic prediction tools. Recent research showed that two different algorithms performed much more poorly in Black and Native American or Alaska Native patients than in White patients.[414] For example, one algorithm had sensitivity of 62.2% for White patients compared with 10.0% for Black patients, and 6.7% for Native American or Alaska Native patients at the 90th percentile of risk. Results were very similar for the other algorithm examined in this study. Future studies of risk prediction tools should carefully assess the performance across racial, ethnic, and other important subgroups, such as age, gender and gender identity, and sexual orientation.

Given the limits of screening instruments and risk prediction tools for predicting suicide risk, the UK's National Institute for Health and Care Excellence guidance on longer-term management of self-harm suggests that clinicians "Do not use risk assessment tools and scales to predict future suicide or repetition of self-harm" and instead recommends conducting a

'needs assessment' to determine allocation of clinical aftercare.[415] Similarly, The Prioritized Research Agenda for Suicide Prevention[416] concluded that "there is great urgency to finding adequate suicide screening approaches for various sectors of medical care" and notes that the "science of screening is lagging behind practice" (p. 25).[416] This group has proposed a number of research needs to help improve suicide risk prediction, including understanding current practice, developing intensive monitoring of lifetime high-risk patients, and testing combinations of potential markers for near-term suicide risk, among other recommendations.

Suicide Prevention Treatment

Although the studies of treatment to prevent suicide included in our review did not demonstrate a benefit and indicated a possible increase in risk for one intervention feasible for wide-spread implementation, the included body of evidence had some important limitations. Chiefly, the control groups for the included studies were usual care, typically including specialty mental health care, which is likely effective in reducing the risk of suicide attempts and deaths. Further, "usual care" was sometimes optimized, such as through increased training or selection of known community experts to act as control group clinicians. The very large study with negative findings enrolled participants based on PHQ-9 scores that had been entered into the electronic medical record, and most of these were in the context of usual depression care. Thus, the applicability of these findings to screening in people without known depression is uncertain. In addition, we excluded studies of people who were seeking treatment in acute care settings due to their suicide risk, as well as studies limited to people with substance use or serious mental health conditions like schizophrenia or bipolar disorder, to enhance applicability of our findings to persons who would be identified through screening in general primary care settings. Thus, we examined a fairly narrow slice of the larger body of suicide prevention intervention trials. Given the need for safety among research participants, it would be very difficult to design a study meeting ethical guidelines has a less intensive control group, so it will always be difficult to determine the absolute effectiveness of suicide prevention interventions.

Broader examination of the literature indicates that some treatment approaches are considered effective evidence-based approaches, such as CBT, dialectical behavioral therapy, pharmacologic treatment, and means restriction.[417-419] For example, a meta-analysis of 32 RCTs[420] found that adults who had received psychological treatment were less likely to attempt suicide during followup compared to those who received pharmacological interventions, general supportive interventions, telephone interviews, or treatment as usual. Another systematic review[421] concluded that interventions that directly targeted suicidal thoughts and behaviors were more effective in reducing suicide attempts and suicide compared to interventions that only addressed these factors indirectly. Psychotropic medications also have an important role to play in suicide prevention. Medications may be used for addressing specific mental health conditions that can increase the risk of suicide such as depression, anxiety, PTSD, and bipolar disorder. In addition, acute administration of ketamine and esketamine have been approved for suicide prevention, with onset of benefit within minutes to hours.[422] However, the risk of adverse effects must still be considered.[423]

In 2020, NIMH stated that one of its high priority research areas is "research aimed at implementing evidence-based practices in routine care"[424] and endorsed the Zero Suicide

approach. The Zero Suicide initiative has developed a framework, roadmap, and implementation toolkit that includes elements addressing all levels of healthcare organizations.[425] One of the elements of this approach is comprehensive suicide risk screening. The elements of Zero Suicide are:

- Lead system-wide culture change committed to reducing suicides
- Train a competent, confident, and caring workforce
- Identify individuals with suicide risk via comprehensive screening and assessment
- Engage all individuals at-risk of suicide using a suicide care management plan
- Treat suicidal thoughts and behaviors directly using evidence-based treatments
- Transition individuals through care with warm hand-offs and supportive contacts
- Improve policies and procedures through continuous quality improvement

According to this model, screening alone would be unlikely to have an impact on suicide rates, but it may be a valuable piece of a whole-system intervention. An observational study of 110 outpatient mental health clinics demonstrated that using the Zero Suicide Initiative practices was associated with lower rates of suicide attempts and deaths.[426] A multisite implementation study is underway examining the efficacy the Zero Suicide Initiative framework of care in six different healthcare systems.[65, 427] It is unclear whether these implementation studies will include broad screening in primary care settings or whether they are focused on mental health settings. However, the findings of the large, included suicide prevention study indicates that further study is needed to determine effective suicide prevention interventions that could be feasible for widespread implementation in healthcare systems.

Screening for Depression, Anxiety, or Suicide Risk Separately Compared With Screening for One or More of These Conditions at the Same Time (Contextual Question 1)

We found no evidence on whether there are relative advantages to screening for a single condition versus multiple conditions simultaneously. One included screening (KQ1) study screened for both depression and anxiety, and found no differences between participants whose clinician received a report showing their symptom profiles and those who did not, but whether this was related to the combined versus single-condition screening approach cannot be determined.[165] The commonly-used PHQ-9 screening tool includes an item addressing suicidal ideation, and while some patients reported having difficulty answering that item (as described above), the performance characteristics of the PHQ were very similar with or without the suicide-related item according to studies included in our review. In addition, among our included studies of anxiety treatment in primary care settings, studies that included people with anxiety or depression generally had smaller effect sizes on both anxiety and depression outcomes than studies that were limited to people with anxiety. This finding could be due to differences across the two groups of studies in mean baseline symptom severity, measures used, or other study characteristics. Our searches did not turn up any additional studies that helped address this question.

Mental Health Equity Across Racial and Ethnic Groups

We found minimal information on the effects of mental health screening in some important specific patient populations. The long history of discriminatory policies and institutions in the US have left an impact on the mental health of traditionally underserved communities, such as among people who identify as Black, Hispanic/Latino, Native American, and Asian American. The health care system has contributed to these inequities through inadvertent biases in diagnosis and by tolerating differential barriers to receiving appropriate treatment. For example, compared to White patients, misdiagnosis of mental health conditions appears to be more common in Black and Hispanic/Latino patients,[87, 88, 428] who are also less likely to receive mental health services than White or Asian Americans.[429, 430] Cost of treatment and lack of insurance are among the main barriers to receiving mental health services,[431] which tend to have a greater impact on Black Americans and other race and ethnic groups than on White Americans, given the structural policies in the US that have contributed to large inequities in wealth.[432] Implementation of routine depression screening may help in reducing inequities that stem from differential screening, as one large implementation study showed that a program of routine screening eliminated disparities between Black and other English-speaking primary care patients in a large health system.[433] See **Appendix H** for a more detailed examination of mental health inequities related to racial and ethnic background. More research is needed on the impact of mental health screening in Black, Hispanic/Latino, Native American, and Asian American communities in the US.

Validity of Screening Instruments Across Race and Ethnic Groups (Contextual Question 5)

Several studies noted similar psychometric properties of English versions of the PHQ-9[91, 434, 435] and the EPDS[436] across different American race and ethnic groups. However, we identified some variation in factor structure for some instruments, and differences in the relative patterns of item endorsement across race and ethnic groups, suggesting that some mental health screeners may perform differentially across cultural groups. For example, one study found a slightly different pattern of symptom endorsement for Chinese American and Hispanic/Latino participants compared to White participants, but no differences between White and Black participants for the PHQ-9.[91] The 20-item CESD showed factor structure variability across American cultural groups in measuring depression,[437, 438] and poorer predictive ability for Black than for White adults. In addition, Black Americans had a different pattern of endorsement of anxiety symptoms on the GAD-7 than White Americans.[90] The GAD-7 factor structure was similar across Black, White, and Hispanic groups, however, indicating a single underlying factor. See **Appendix H** for a more detailed discussion on the validity of screening instruments across race and ethnic groups.

Mental Health Screening and Increased Recognition or Treatment of Depression (Contextual Question 2)

Some of the depression screening trials reported on whether screening increased the likelihood that patients' depression was recognized by their providers, whether they were offered treatment

or referred for treatment, and whether they received treatment (**Appendix I**). Five studies of depression screening reported on whether screening increased the likelihood that patients' depression was recognized by their clinician, typically measured by the presence of a diagnosis in the medical record.[153, 155, 159, 164, 439] Four of these five studies found an increased likelihood of clinician recognition, covering general, older, and perinatal populations.[153, 155, 159, 164] Three studies reported an increased likelihood of receiving psychological treatment for depression, among perinatal[159, 164] and general adult populations.[152] However, three other studies reported on whether patients were advised or referred for psychological treatment, and while they found effects in the direction of benefit, none of these findings were statistically significant.[149, 151, 163] Eight trials reported on prescriptions for or use of antidepressant medications. Across all populations, studies were evenly split between finding an increased likelihood of antidepressant prescription or use and finding no group differences (among general,[149-152] older,[155, 157] and perinatal[161, 164] populations). None of the studies of anxiety or suicide risk screening reported on these outcomes.

Healthcare System Supports to Ensure Appropriate Diagnosis, Followup, and Treatment (Contextual Question 3)

Relatedly, an ongoing issue of concern has been ensuring that primary care patients who are identified as needing mental health services receive the appropriate mental health care. This concern is expressed in the current USPSTF recommendations on screening for depression, which state "Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate followup."[133] Integrated care models, such as collaborative care, have been designed to help address gaps in access to mental health treatment in primary care through the addition of behavioral health professionals (on- or off-site). Collaborative care programs use a multidisciplinary approach that includes behavioral health and psychiatric consultation within the care team. This model of care focuses on population-based care, patient-centered goal setting, stepped care, and measurement-based assessment.[440-442] Collaborative Care programs have been shown to be more effective than usual care for the initiation of treatment and improved outcomes for depression and anxiety.[443-447] For example, a 2012 Cochrane Collaboration review of 29 randomized trials (N=24,308) found Collaborative Care resulted in greater depression response (RR 1.32 [95% CI, 1.22 to 1.43], anxiety response (RR 1.50 [95% CI, 1.21 to 1.87]), and antidepressant medication use (RR 1.45 [95% CI, 1.33 to 1.63[447]]) compared with usual care at zero to six months. A 2021 IPDMA identified that while collaborative care has been shown to reduce suicidal ideation in patients with depression compared with usual care, the overall effect size is small[448] (SMD, −0.11 [95% CI, −0.15 to −0.08]).

Patient education, shared decision making, and family supports within Collaborative Care models can be used to increase patient and family involvement in the management of depression and anxiety.[440] A systematic review from 2020 of Collaborative Care programs found that the most common engagement strategies employed across programs were patient education (87%) and self-management/self-help supports (47%). Care managers were largely responsible for delivering patient and family engagement and supports with engagement occurring most frequently within the first six- or twelve-months following treatment initiation.[440]

The use of Collaborative care has been shown to improve the initiation of mental health care for individuals in traditionally underserved racial and ethnic groups, with the largest amount of evidence supporting benefits in Black and Hispanic/Latino patients.[449-451] A systematic review from 2020 found that among 12 studies comparing collaborative care to usual care for Black, Hispanic/Latino, Native, and Asian American patients, eight showed evidence for a benefit in depression symptoms.[451] For example, one study of 400 primarily Hispanic/Latino adults in Los Angeles found that a culturally adapted CBT delivered through collaborative care showed significantly lower PHQ-9 scores at 16 weeks compared with usual care (8.6 vs 13.3, $p<0.001$).[452] For patients with limited English proficiency, collaborative care delivered by bilingual providers may be more effective than usual care. Within a 2018 systematic review, three of four high-quality RCTs reported that 13 to 25 percent more patients had improved depressive symptoms when treated with culturally tailored collaborative care compared to usual care.[450]

Despite these benefits shown by integrated care models, most care settings report insufficient resources to address the needs of the large number of patients in primary care. Telemedicine may offer an opportunity for integrated care within rural and lower resourced care settings. Remote Collaborative Care teams have shown effectiveness in treating depression and anxiety across settings.[453] While the spread of telemedicine may help increase access to these integrated behavioral and medical care programs in mental health, it may also be a driver of disparities in access to care, particularly among lower SES populations;[442] therefore, flexibility in treatment setting will remain important.

Limitations of Our Approach

This report is not an exhaustive review of all evidence related to screening for depression, anxiety, and suicide risk. Given time and resource constraints, we focused on the evidence necessary to support the USPSTF in making a recommendation. That is, we made a priori decisions to focus this review on evidence to determine: whether screening in primary care (or similarly broad) populations improves health outcomes or causes harm; whether there are screening tools that are valid and feasible to use in primary care populations; and whether there are treatments available for persons with these conditions that are effective and not harmful. We did not aim to determine all possible screening instruments and treatments and their comparative effectiveness. We also excluded studies in narrow populations that were not widely applicable to screening in primary care settings, but are seen regularly in primary care settings nevertheless. For example, we did not include studies limited to persons with physical or developmental disabilities or to people with medical or other mental health comorbidities such as heart disease, cancer, substance use disorders, bipolar disorder, or PTSD. Similarly, the screening instruments selected for review may not apply to some important groups of patients, such as those with low literacy, low health literacy, limited verbal language, or patients who do not speak English. We also did not aim to provide an exhaustive exploration of variability in treatment effects and instrument accuracy across all possible patient subgroups and settings. As such, we can provide little guidance on matching tools and treatment to individual patient characteristics, nor can we provide guidance on specific necessary and sufficient intervention components. We also did not examine intervention approaches other than psychological and

FDA approved pharmacologic agents. There may be other interventions that could be beneficial, such as physical activity. We also did not include examination of some potentially valuable intervention tools such as virtual reality programs unless they were embedded in a broader psychological intervention.

For the accuracy of suicide risk screening tools, our review focused on tools to determine the presence of suicidal ideation, but we did not address the ability of these tools to predict future suicide attempts and deaths. Risk prediction requires a more extensive, multi-dimensional approach that would likely not be feasible for broad screening in primary care settings. We provide information above on a separate body of literature on the accuracy of tools to predict suicide attempts and deaths.

While not widely used to our knowledge, tools have been developed that simultaneously screen for anxiety, depression, or suicide risk with a single instrument, such as the 21-item DASS-21. Among adults from a virtual behavioral healthcare setting,[454] the depression and anxiety domains of the DASS-21 were strongly correlated with the PHQ-8 and the GAD-7, respectively. We did not, however, include test accuracy evidence for the DASS-21 or other combined screening instruments. While we recognize the utility of a single screening instrument, in practice these multi-condition instruments typically have a set of questions for each condition that are scored separately and would be similar to administering the PHQ and the GAD at the same clinical encounter.

Another limitation of our review is that, for the harms of included medications, we focused on synthesized literature published in the past 5 years, with the exception of some Cochrane reviews of well-established medications. In addition, we examined only observational studies published in our search window. To help mitigate these limitations, we supplemented our evidence with information from FDA safety monitoring materials in the Discussion above.

Limitations of the Studies and Future Research Needs

For depression screening, there is still uncertainty about the benefits of screening in older adults, and studies are needed that report outcomes using instruments specifically designed for older adults, and both short-term (<6-month) and long-term (2 years or more) outcomes. There are also limitations to our understanding of the direct impact of screening relative to other depression management supports. As depression screening becomes the standard of care, this is increasingly difficult to study. Nevertheless, rigorous examination of implementation programs are needed that report the percent of patients being screened, referred, and treated as well as patient health outcomes such as depression symptoms and quality of life, prior to program implementation and in control clinics. In addition, more research is needed to understand the impact of depression screening and most appropriate tools among Black, Hispanic/Latino, Asian-American, and Native American/Alaska Native communities. Native Americans/Alaska Native communities were not represented in the included studies, despite disproportionately high depression prevalence. Similarly, more information is needed on screening in other underrepresented groups such as gender non-conforming, immigrant, and non-English speaking communities. Relatedly, research is needed on whether implicit bias among primary care

clinicians is associated with lower likelihood of screening some patients or the likelihood of appropriate diagnosis and treatment.

For anxiety screening, more studies are needed on the diagnostic accuracy of screening tools that are feasible for use in primary care settings, tested among primary care patients or similar populations, using valid reference standards, and determining (and replicating) optimal cutoffs for any anxiety disorder. Additionally, more studies are needed that specifically address panic disorder and social anxiety disorder, where evidence was the weakest.

The evidence base to support broad suicide screening in primary care settings is limited and indicates that some approaches may be unhelpful or even potentially harmful. Foundational research is urgently needed in primary care populations, including determining which tools should be used, how screening should be implemented, and what interventions should be provided to people who screen positive. For example, what training is needed and for whom, what system-level supports are needed, and how to minimize the risk of harms such as feeling judged or stigmatized, feeling that a cry for help was ignored, or suffering unnecessary loss of autonomy. We support the NIMH call for research examining the use of the Zero Suicide approach described above under "Suicide prevention treatment." Patients who are considering suicide are seen in primary care settings on a regular basis, but it is important to determine what approaches are effective in helping these patients before making recommendations.

We identified several studies currently underway that address depression, anxiety, and suicide screening (**Appendix J Table 1**). Seven studies address implementation of depression screening programs, three of which focus on the effects of depression screening feedback to the patient or primary care clinician on depression severity, and three that address both depression and anxiety screening in perinatal populations. Two studies were identified that address suicide screening and focus on quality improvement within health systems where suicide-related interventions were previously implemented.

Conclusions

Both direct and indirect evidence support depression screening in primary care settings, including during pregnancy and postpartum. While there is clear evidence that treatment for anxiety is beneficial, there are important evidence gaps surrounding the direct benefits of screening and the best screening tools. There are numerous important gaps in the evidence for suicide risk screening in primary care settings.

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Figure 1. Analytic Framework

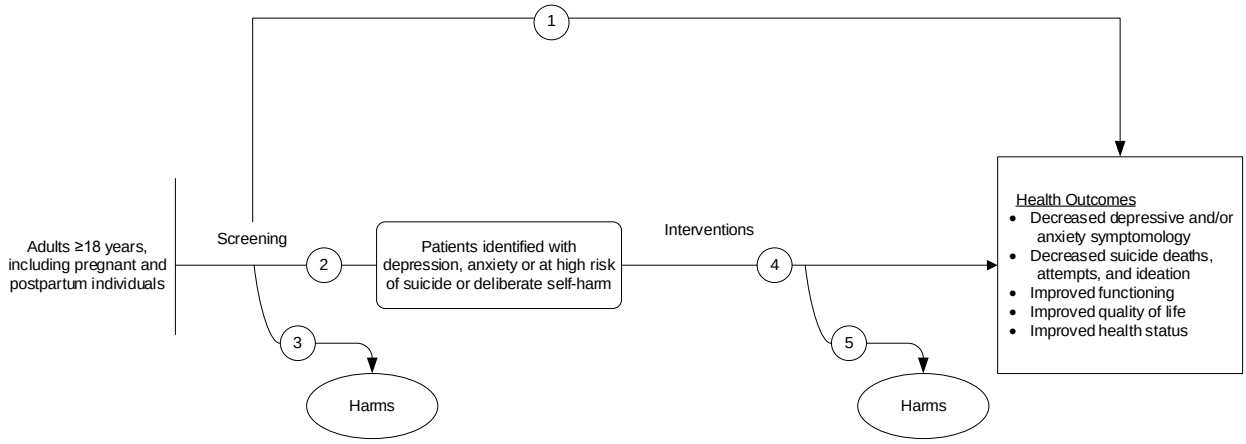
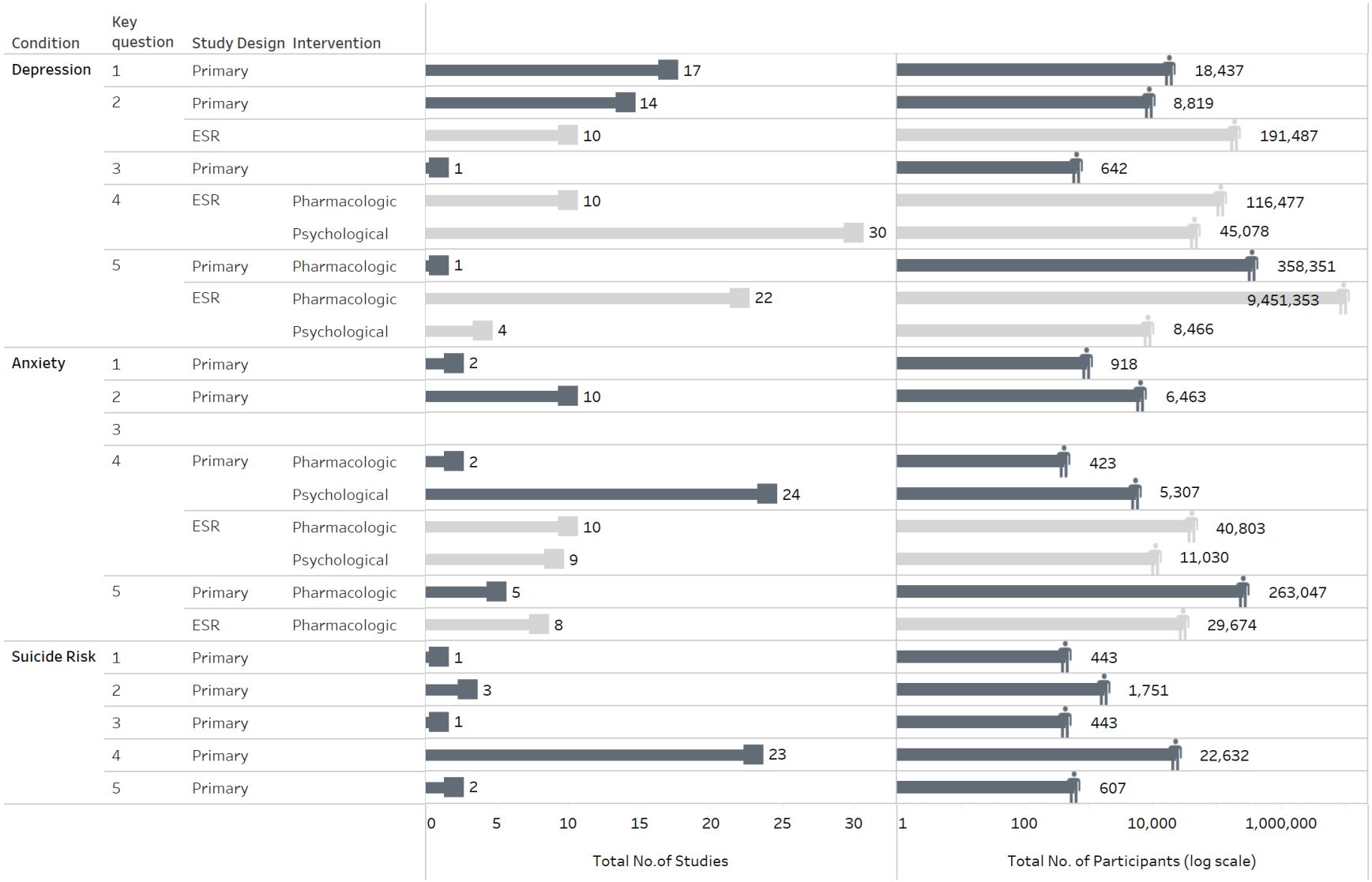
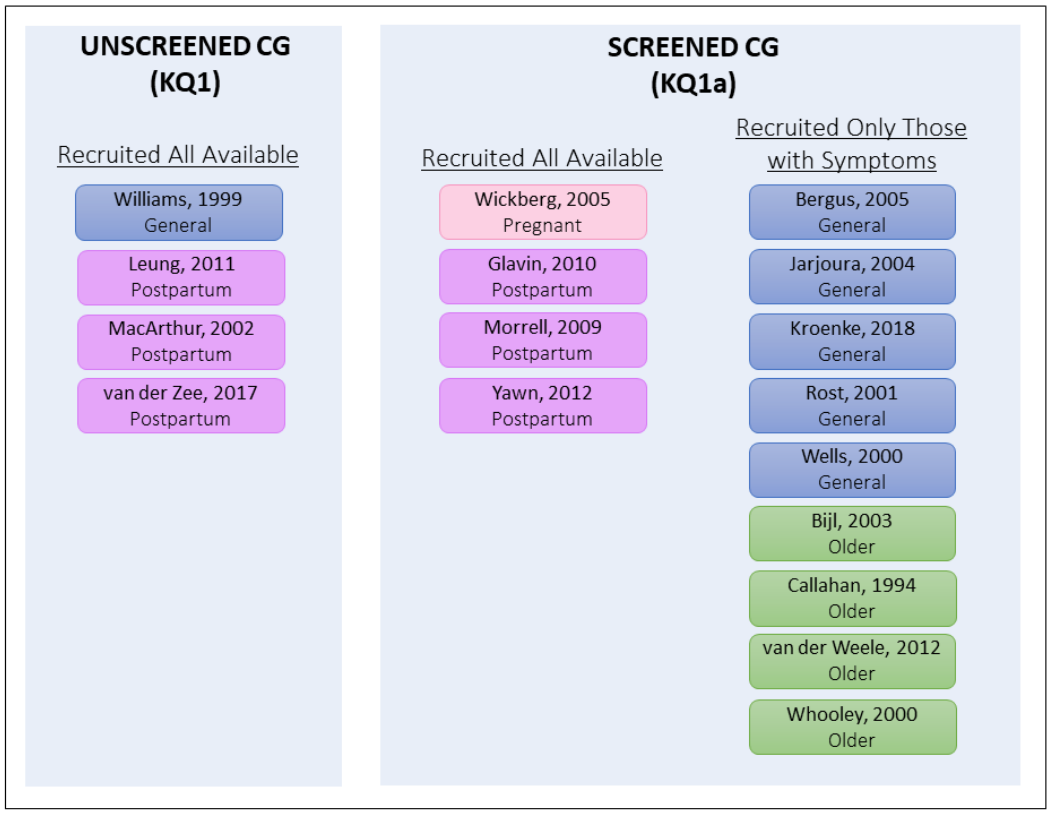


Figure 2. Overview of Included Studies



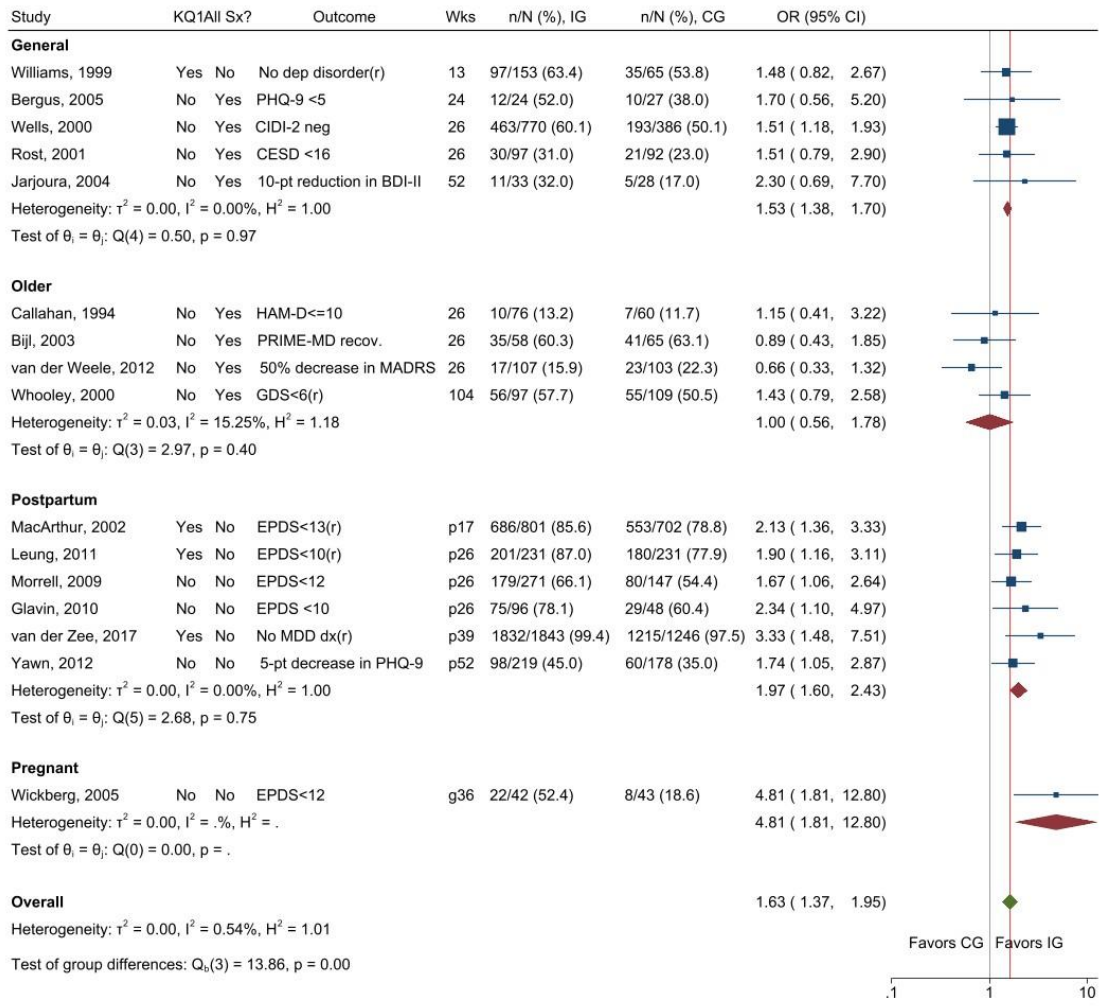
NOTE: Studies may be counted under multiple Key Questions and/or conditions.
Abbreviations: ESR = existing systematic review; no. = number.

Figure 3. Key Study Design Features Among Depression Screening Studies (KQ1)



Abbreviations: CG = control group; KQ = key question.

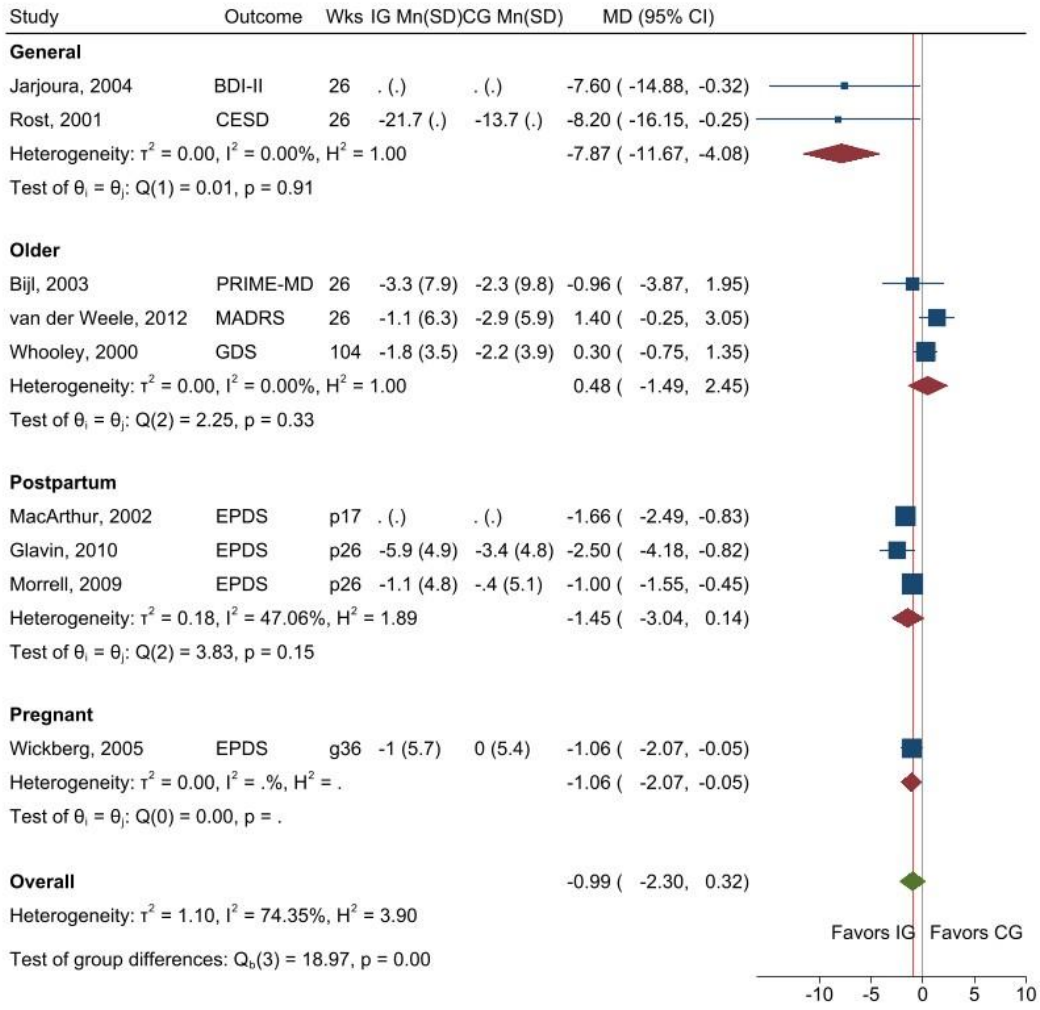
Figure 4. Forest Plot Showing a Combined Outcome Representing Reduced Depression From Depression Screening Studies (KQ1): Depression Remission or Scoring Below a Cutoff, Depression Prevalence or Scoring Above a Cutoff (Reversed), and Depression Response



(r)Reversal of a study-provided result from above to below cutoff

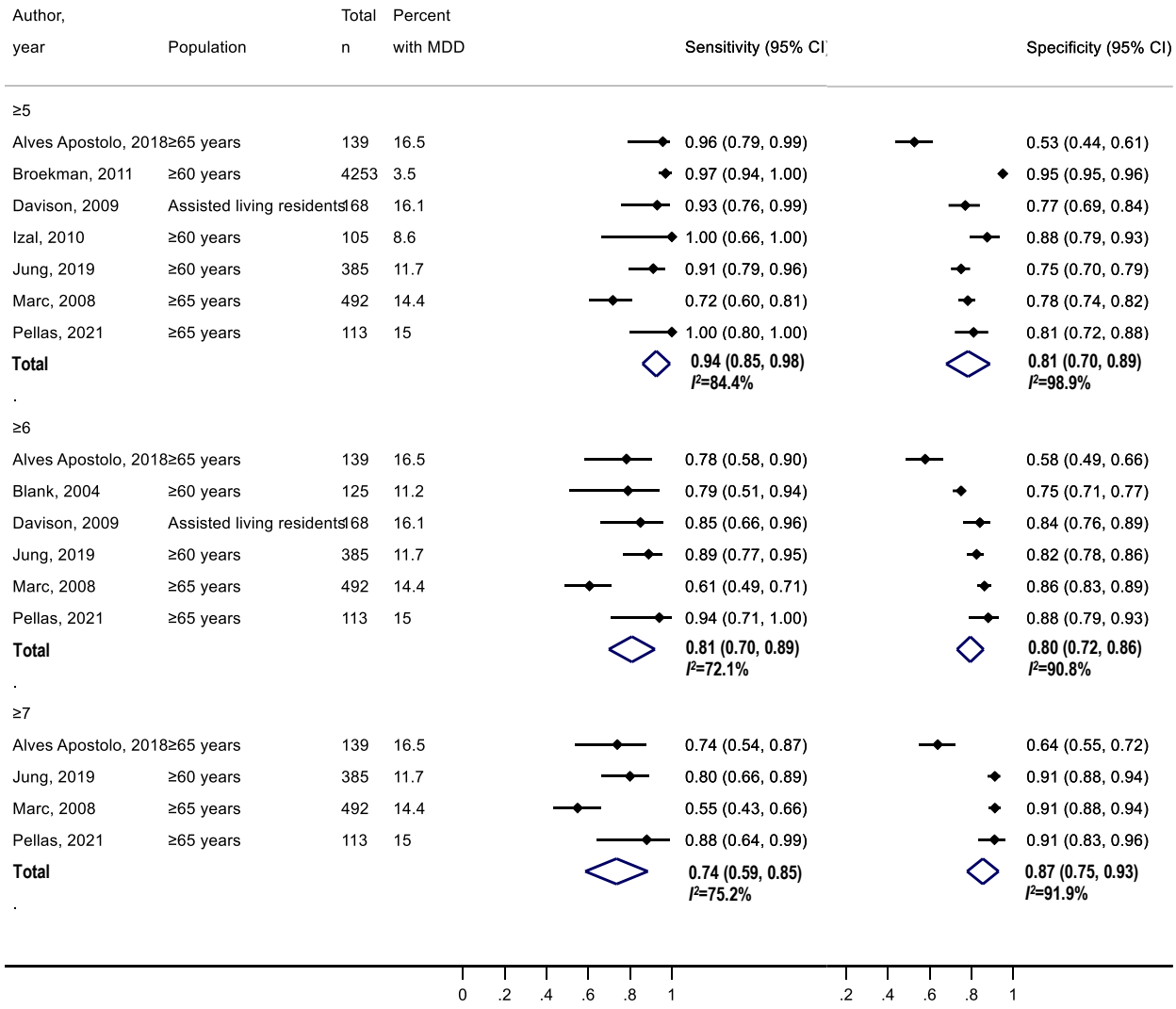
Abbreviations: BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression scale; CIDI = Composite International Diagnostic Interview; CG = control group; CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale; GDS = Geriatric Depression Scale; HAM-D = Hamilton Rating Scale for Depression; IG = intervention group MADRS = Montgomery–Asberg Depression Rating Scale; MDD = major depressive disorder; OR = odds ratio; PHQ = Patient Health Questionnaire; PRIME-MD = Primary Care Evaluation of Mental Disorders.

Figure 5. Forest Plot Showing the Difference Between Groups in Change From Baseline Depression Symptom Score in Depression Screening Studies (KQ1)



Abbreviations: BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression scale; CG = control group; CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale; GDS = Geriatric Depression Scale; IG = intervention group; MADRS = Montgomery–Asberg Depression Rating Scale; MD = mean difference; NR = not reported; PRIME-MD = Primary Care Evaluation of Mental Disorders.

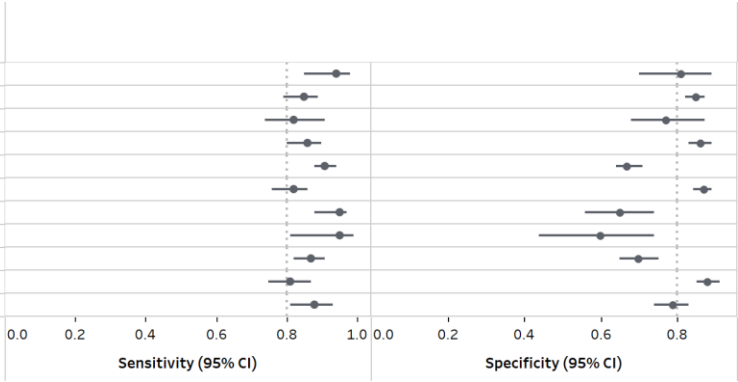
Figure 6. Test Accuracy of the GDS-15 to Detect MDD, at Cutoffs of 5, 6, and 7 (KQ2)



Abbreviations: CI = confidence interval; MDD = major depressive disorder.

Figure 7. Summary of Included ESR and Primary Evidence for Test Accuracy of Screening Instruments to Detect Depression (KQ2)

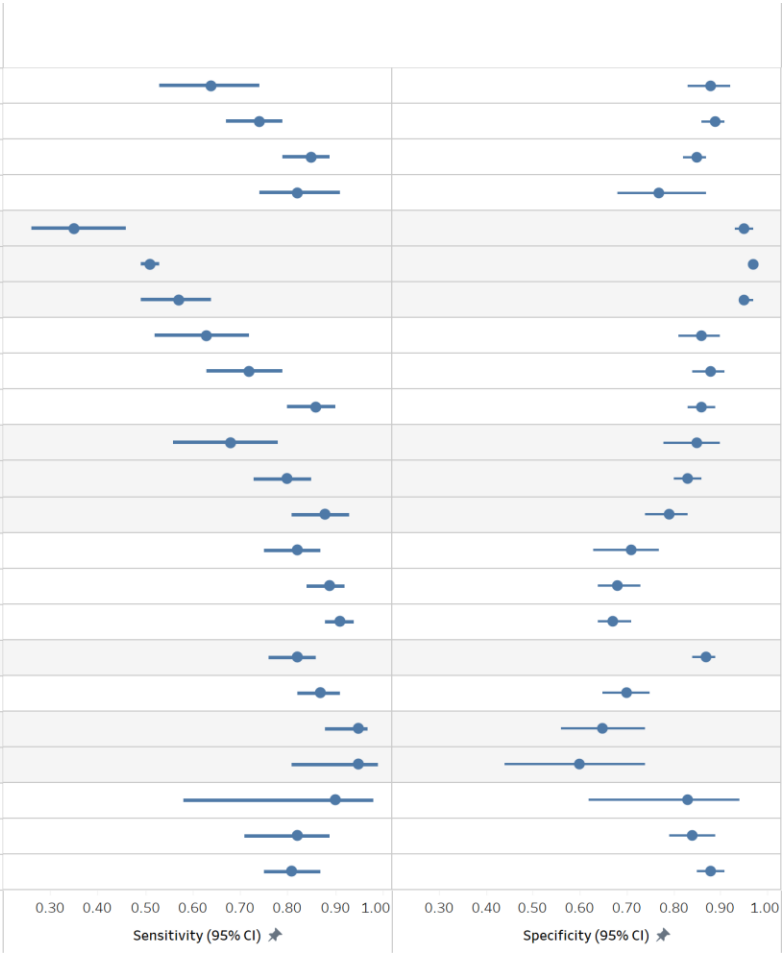
Condition	Screening Test	Population	No. of studies	No. of participants	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)
Major Depression	GDS-15	Older Adults	7	5,655	≥5	0.94 (0.85, 0.98)	0.81 (0.70, 0.89)
	PHQ-9	Adults	100	44,503	≥10	0.85 (0.79, 0.89)	0.85 (0.82, 0.87)
		Pregnant/Postpartum Women	3	1,465	≥10	0.82 (0.74, 0.91)	0.77 (0.68, 0.87)
	PHQ-8	Adults	54	16,742	≥10	0.86 (0.80, 0.90)	0.86 (0.83, 0.89)
	PHQ-2	Adults	100	44,318	≥2	0.91 (0.88, 0.94)	0.67 (0.64, 0.71)
	PHQ-2+PHQ-9	Adults	100	44,318	≥2/≥10	0.82 (0.76, 0.86)	0.87 (0.84, 0.89)
	Whooley	Adults	10	4,618	NA	0.95 (0.88, 0.97)	0.65 (0.56, 0.74)
		Pregnant Women	5	1,402	NA	0.95 (0.81, 0.99)	0.60 (0.44, 0.74)
	CES-D	Adults	28	10,617	≥16	0.87 (0.82, 0.91)	0.70 (0.65, 0.75)
	EPDS	Pregnant Women	58	15,557	≥11	0.81 (0.75, 0.87)	0.88 (0.85, 0.91)
	PHQ-4	Adults	75	34,698	≥4	0.88 (0.81, 0.93)	0.79 (0.74, 0.83)



Abbreviations: CES-D = Center for Epidemiologic Studies Depression scale; CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale; GAD = Generalized Anxiety Disorder; GDS = Geriatric Depression Scale; GDS-SI = Geriatric Depression Scale – Suicide Ideation; NA = not applicable; PHQ = Patient Health Questionnaire; SDDS-PC = Symptom Driven Diagnostic System for Primary Care.

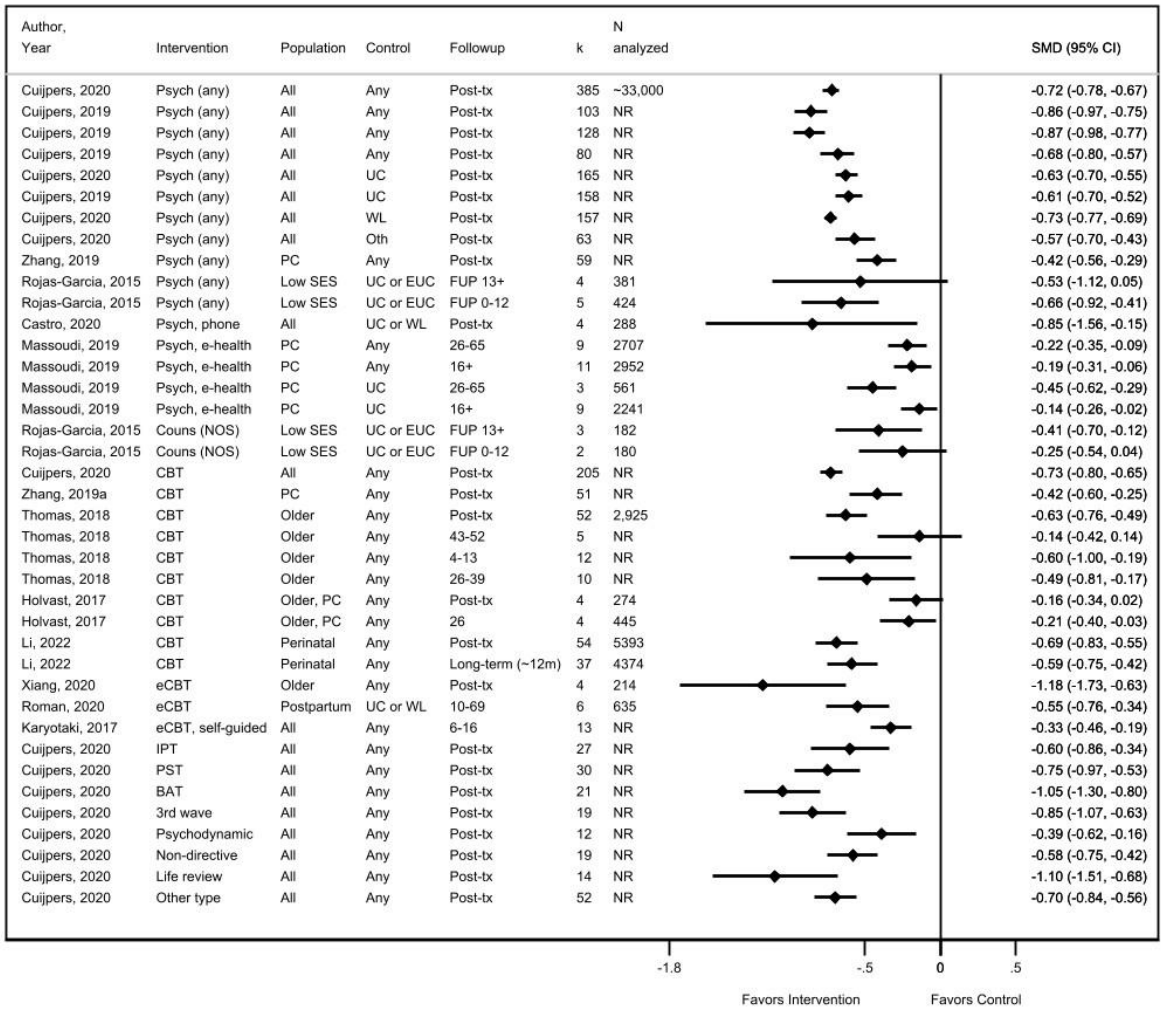
Figure 8. Test Accuracy of PHQ, CES-D, Whooley, and the EPDS From Published SERs (KQ2)

Screening test	Author, year	Reference standard	No. of studies	No. of participants	Cutoff
PHQ-9 Linear	Negeri, 2021	Fully structured diagnostic interview	20	17167	≥10
		MINI	33	16102	≥10
		Semi-structured diagnostic interview	47	11234	≥10
	Wang, 2021 (prenatal)	Fully/Semi-structured diagnostic interview	3	1465	≥10
PHQ-9 Algorithm	He, 2020	Fully structured diagnostic interview	13	7577	Original
		MINI	14	2780	Original
		Semi-structured diagnostic interview	27	6331	Original
PHQ-8	Wu, 2020	Fully structured diagnostic interview	13	7596	≥10
		MINI	14	2784	≥10
		Semi-structured diagnostic interview	27	6362	≥10
PHQ-4	Harel, 2022	Fully structured diagnostic interview	15	12109	≥4
		MINI	31	14870	≥4
		Semi-structured diagnostic interview	29	7719	≥4
PHQ-2	Levis, 2020	Fully structured diagnostic interview	20	17319	≥2
		MINI	32	15296	≥2
		Semi-structured diagnostic interview	48	11703	≥2
PHQ-2+PHQ-9	Levis, 2020	Semi-structured diagnostic interview	44	10627	≥2 (PHQ-2), ≥10 (PHQ-9)
CES-D	Vilagut, 2016	Standardized diagnostic interview	22	NR	≥16
Whooley	Bosanquet, 2015	Diagnostic interview	10	4618	NA
	Smith, 2022 (prenatal)	Diagnostic interview	5	1402	NA
EPDS	Levis, 2020	Fully structured diagnostic interview	4	3188	≥11
		MINI	18	3302	≥11
		Semi-structured diagnostic interview	36	9066	≥11



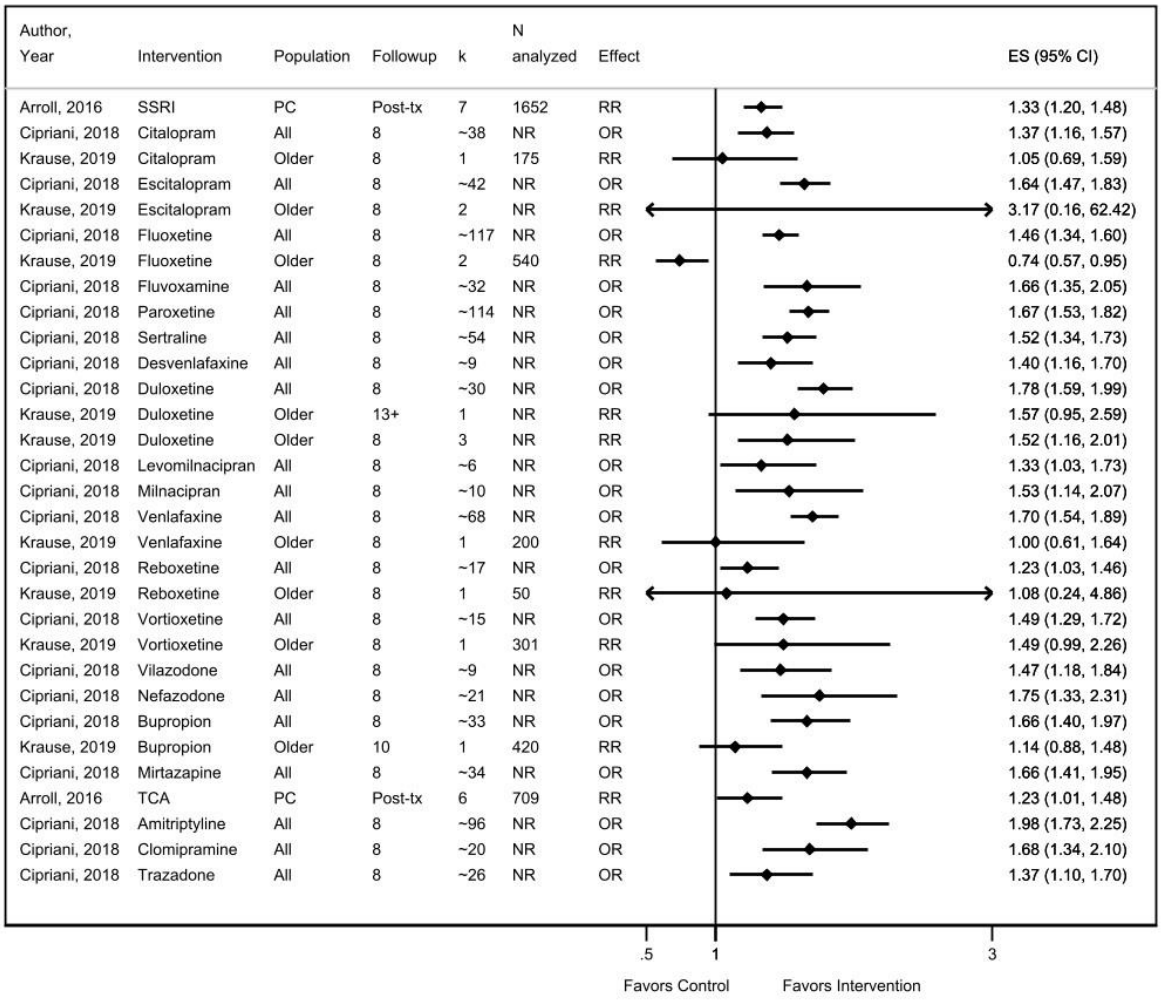
Abbreviations: CES-D = Center for Epidemiologic Studies Depression scale; CI = Confidence interval; EPDS = Edinburgh Postnatal Depression Scale; MINI = Mini International Neuropsychiatric Interview; NA = Not applicable; NR = Not reported; PHQ = Patient Health Questionnaire; SER = systematic evidence review.

Figure 9. Forest Plot of Standardized Mean Differences Between Groups in Depression Symptom Severity by Intervention Type, Population, Control Group Type, and Followup for Psychological Treatment of Depression (KQ4)



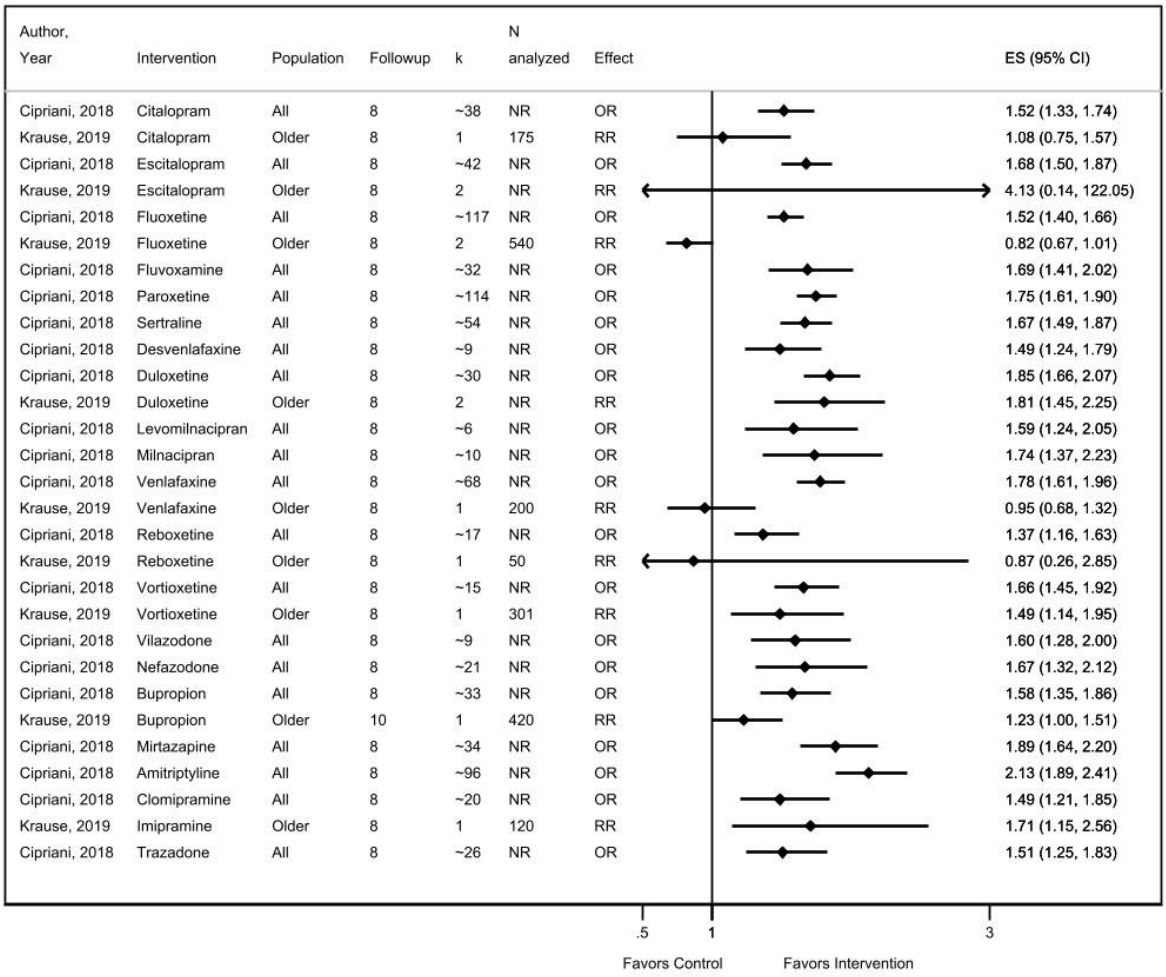
Abbreviations: BAT = Behavioral Activation Therapy; CBT = cognitive behavioral therapy; CI: confidence interval; eCBT = enhanced cognitive behavioral therapy; EUC = enhanced usual care; IPT = interpersonal therapy; NOS = not otherwise specified; NR = not reported; PC = primary care; PST = problem solving therapy; SES = socioeconomic status; SMD = standardized mean difference; UC = usual care; WL = waitlist.

Figure 10. Forest Plot of Group Differences in Depression Remission With Pharmacological Treatment of Depression Compared to Placebo (KQ4)



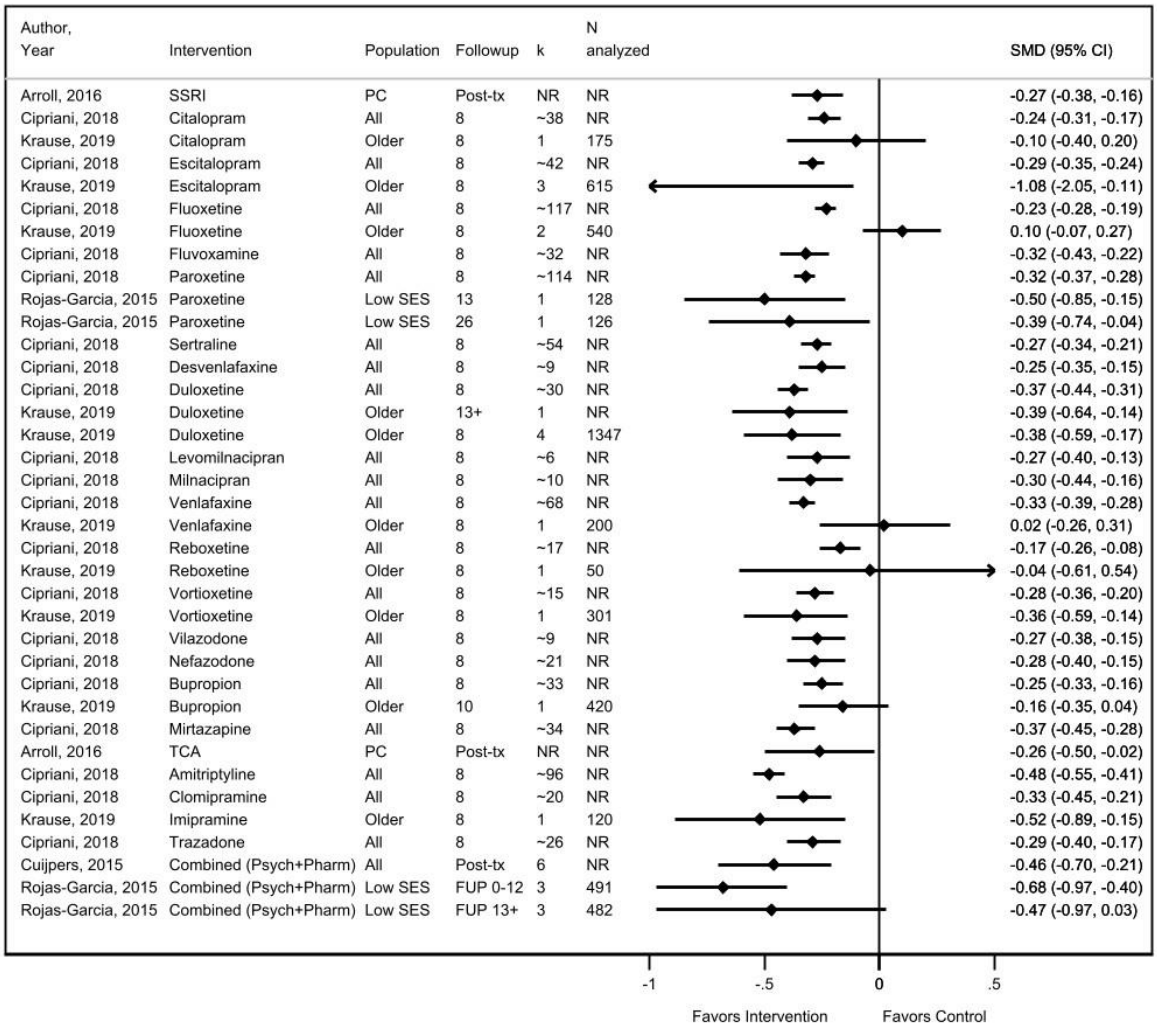
Abbreviations: CI = confidence interval; ES = effect size; NR = not reported; OR = odds ratio, PC = primary care; RR = relative risk; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Figure 11. Forest Plot of Group Differences in Depression Response With Pharmacological Treatment of Depression Compared to Placebo (KQ4)



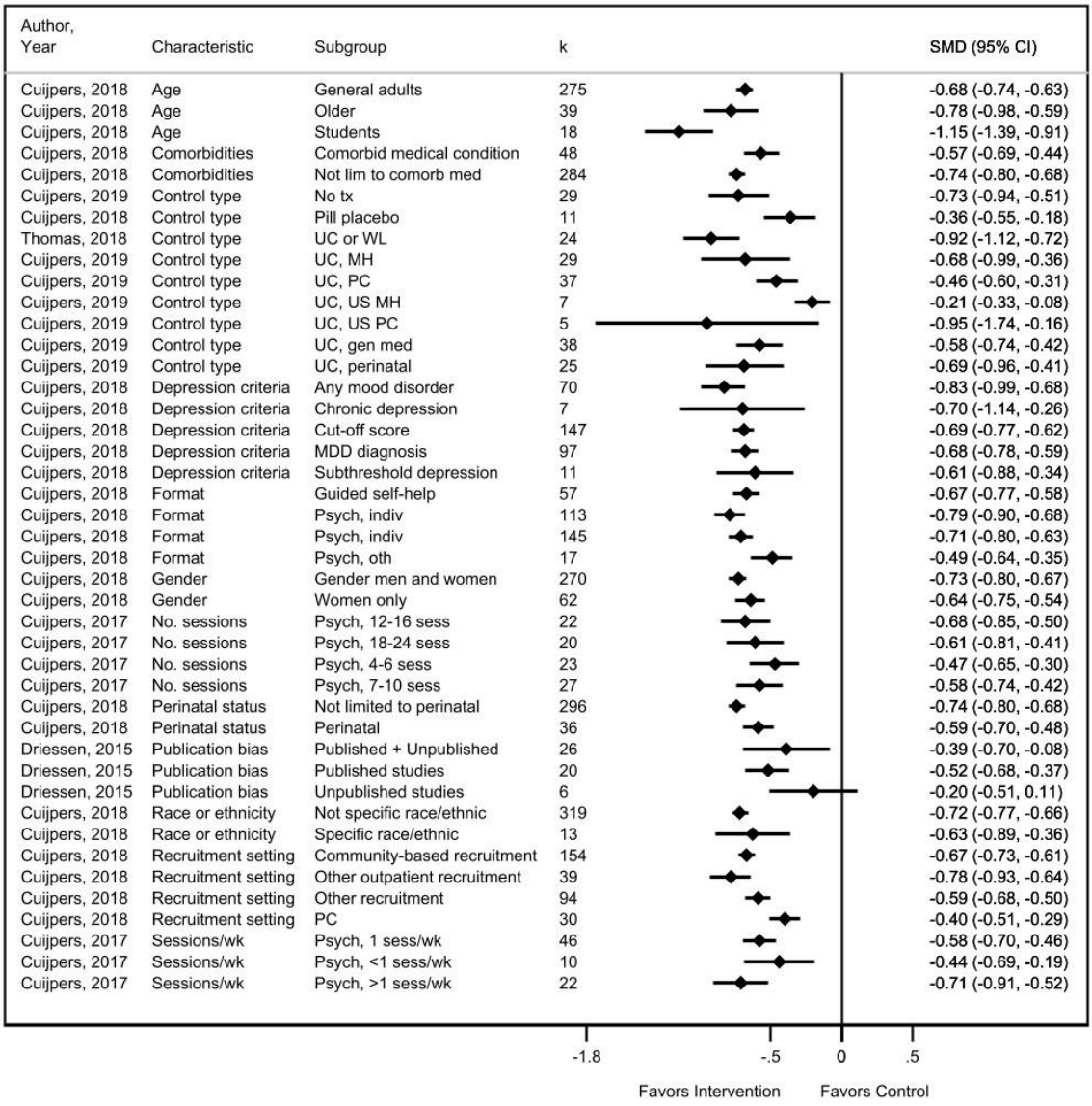
Abbreviations: CI = confidence interval; ES = effect size; NR = not reported; OR = odds ratio, RR = relative risk.

Figure 12. Forest Plot of Standardized Mean Differences Between Groups in Depression Symptom Severity for Pharmacological Treatment of Depression Compared to Placebo (KQ4)



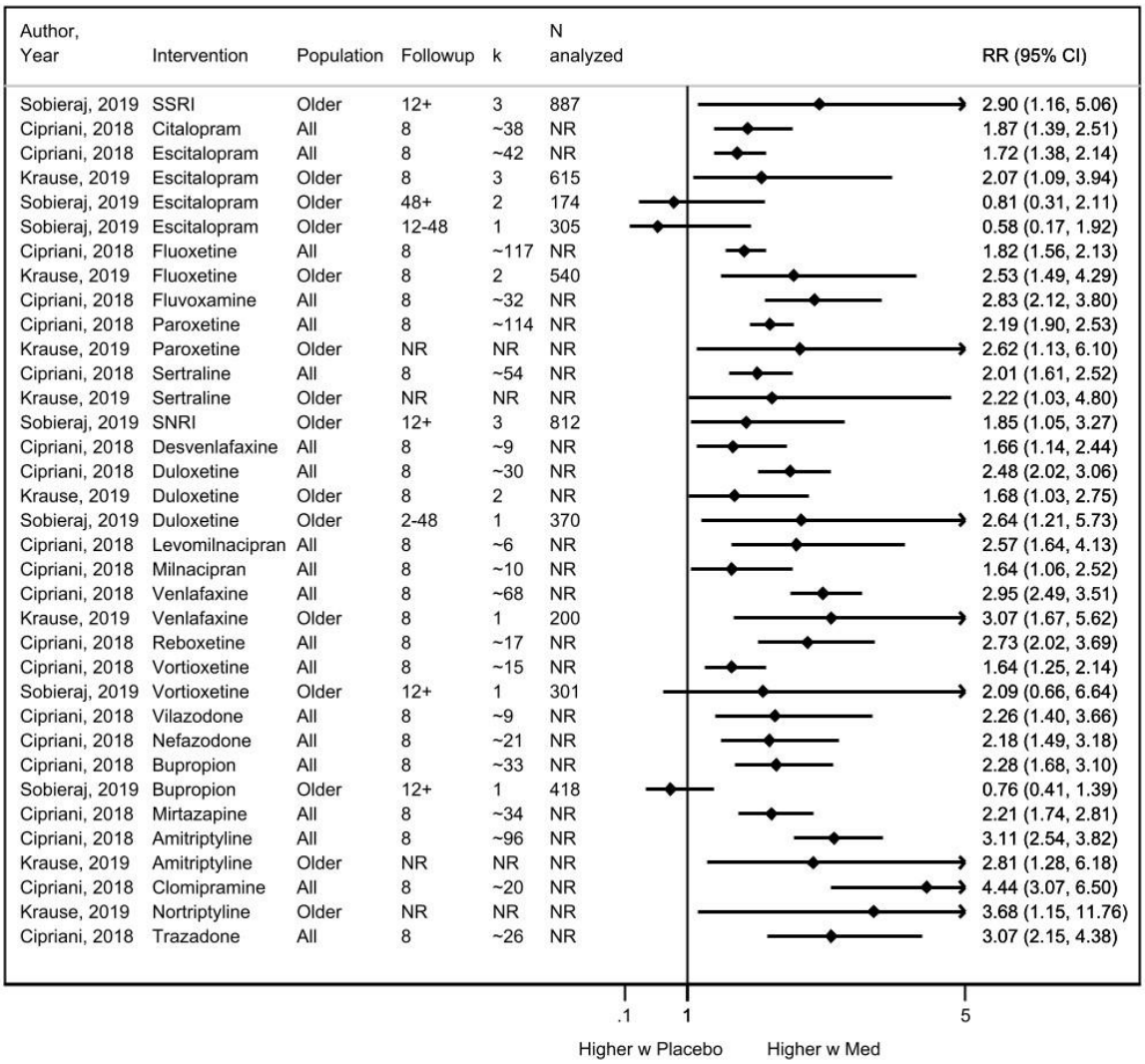
Abbreviations: CI: confidence interval; FUP = followup; NR = not reported; OR = odds ratio, PC = primary care; RR = relative risk; SES = socioeconomic status; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Figure 13. Forest Plot of Standardized Mean Differences Between Groups in Depression Symptoms Severity by Study, Intervention, and Population Characteristics Where Effect Modification Was Assessed for Psychological Treatment of Depression (KQ4)



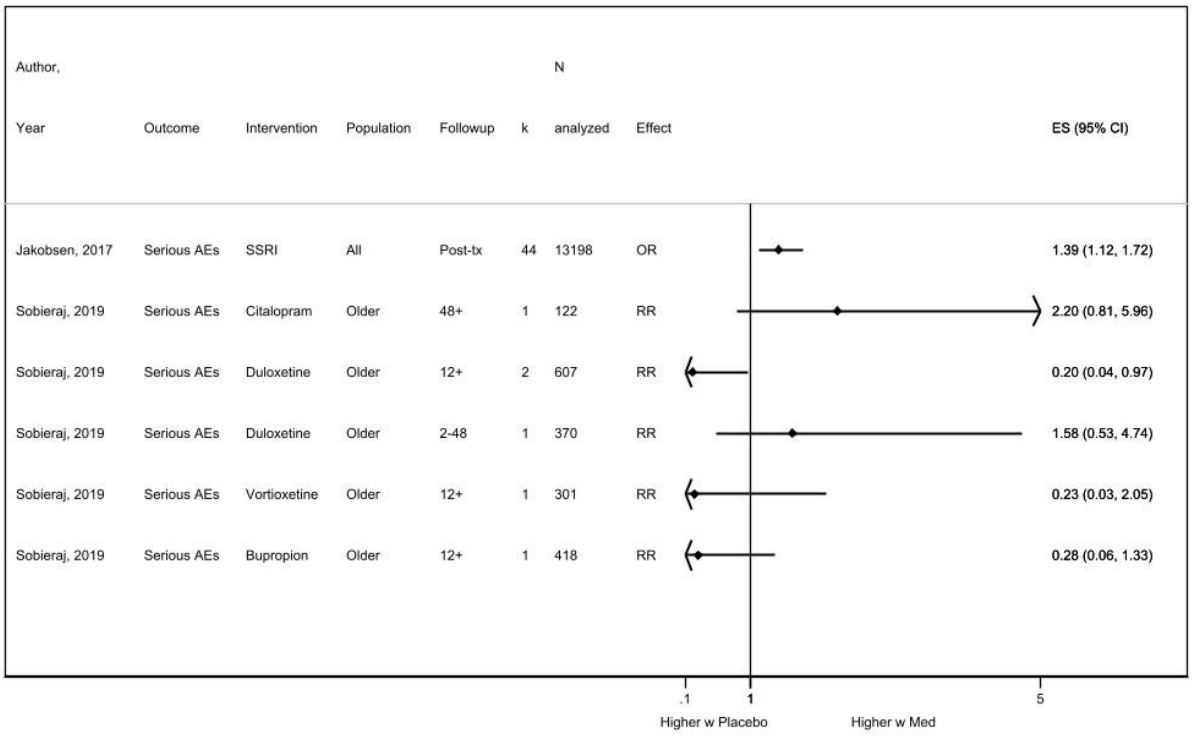
Abbreviations: CI = confidence interval; MDD = major depressive disorder; MH = mental health; PC = primary care; SMD = standardized mean difference; UC = usual care; WL = wait list.

Figure 14. Forest Plot of Group Differences in Dropout Due to Adverse Events With Pharmacological Treatment of Depression Compared to Placebo (KQ5)



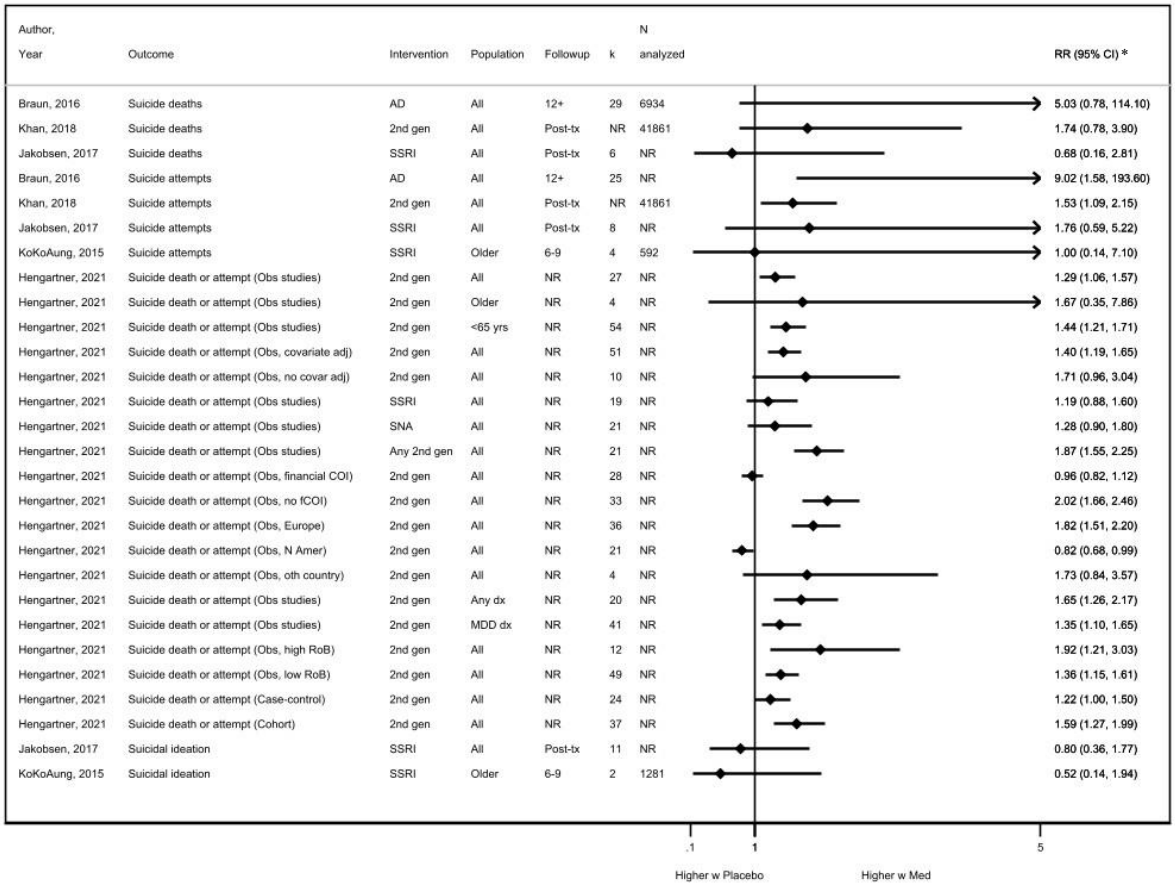
Abbreviations: CI = confidence interval; NR = not reported; RR = relative risk; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitor.

Figure 15. Forest Plot of Group Differences in Any Serious Adverse Events With Pharmacological Treatment of Depression Compared to Placebo (KQ5)



Abbreviations: AE = adverse event; ES = effect size; CI = confidence interval; NR = not reported; OR = odds ratio; RR = relative risk; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitor.

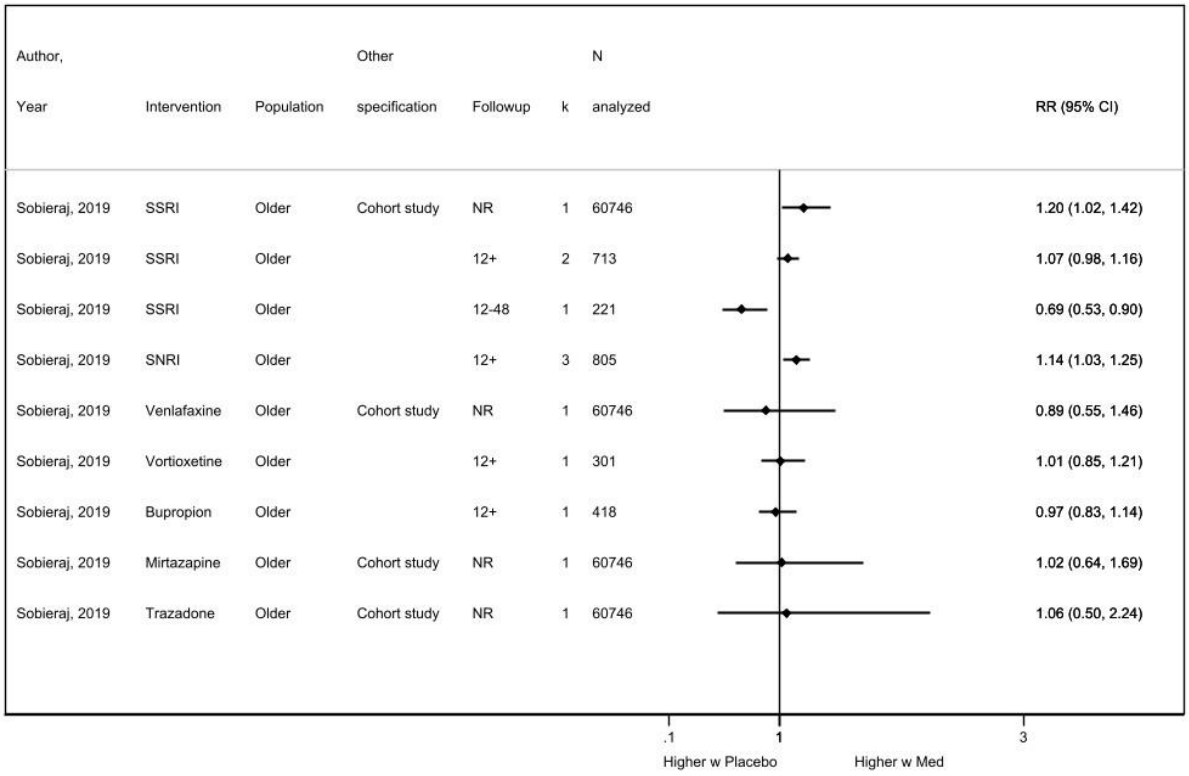
Figure 16. Forest Plot of Group Differences in Suicide-Related Outcomes With Pharmacological Treatment of Depression Compared to Placebo (KQ5)



*The following effects are ORs rather than RRs: suicide deaths with 2nd generation antidepressants; suicide attempts with 2nd generation antidepressants; suicide attempts with SSRIs for older adults; suicidal ideation with SSRIs for older adults.

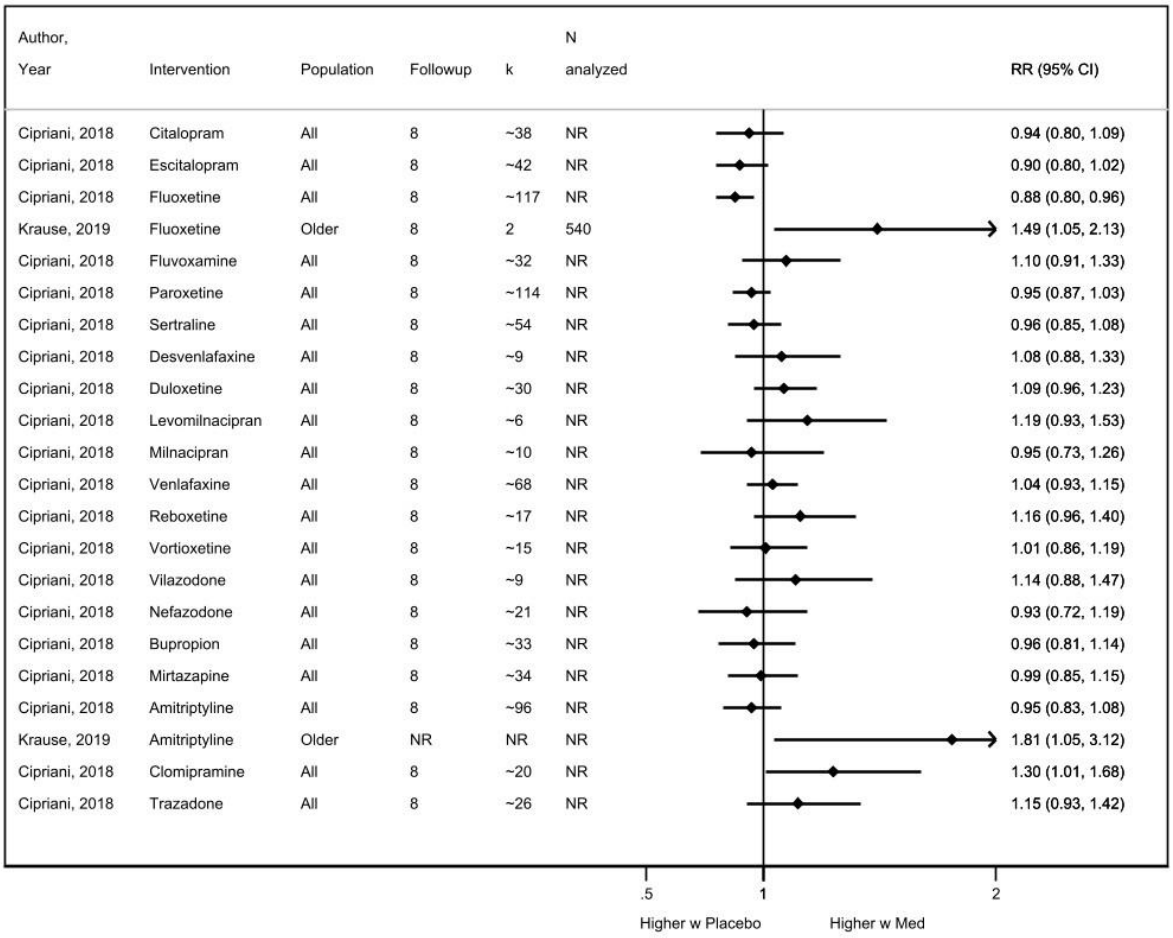
Abbreviations: AD = antidepressant; COI = conflict of interest; MDD = major depressive disorder; NR = not reported; SNA = serotonergic-noradrenergic antidepressant; SSRI = selective serotonin reuptake inhibitor; RR = relative risk.

Figure 17. Forest Plot of Group Differences in Any Adverse Events With Pharmacological Treatment of Depression Compared to Placebo (KQ5)



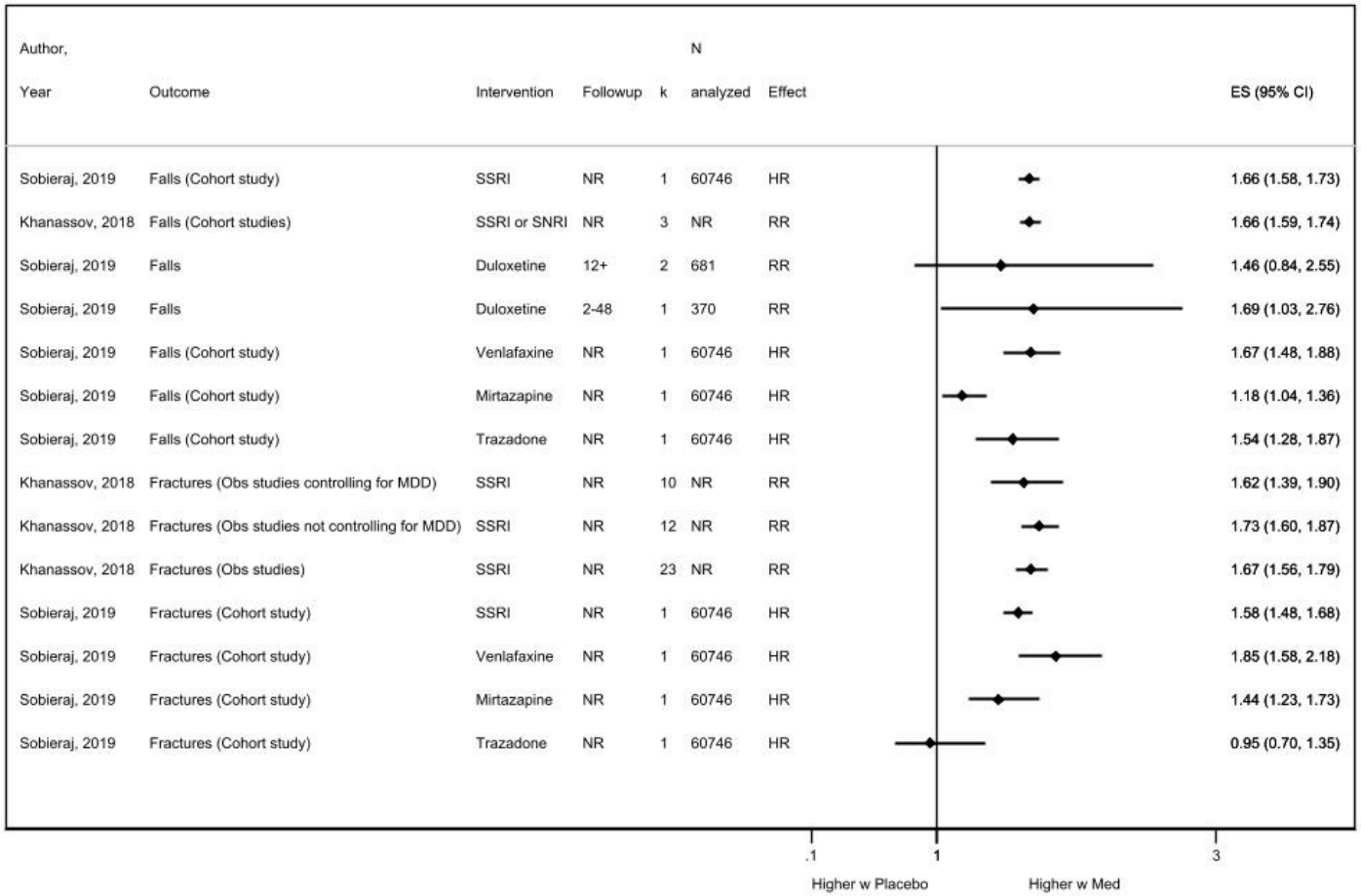
Abbreviations: CI = confidence interval; NR = not reported; RR = relative risk; SNRI = Serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitor.

Figure 18. Forest Plot of Group Differences in Dropout for Any Reason With Pharmacological Treatment of Depression Compared to Placebo (KQ5)



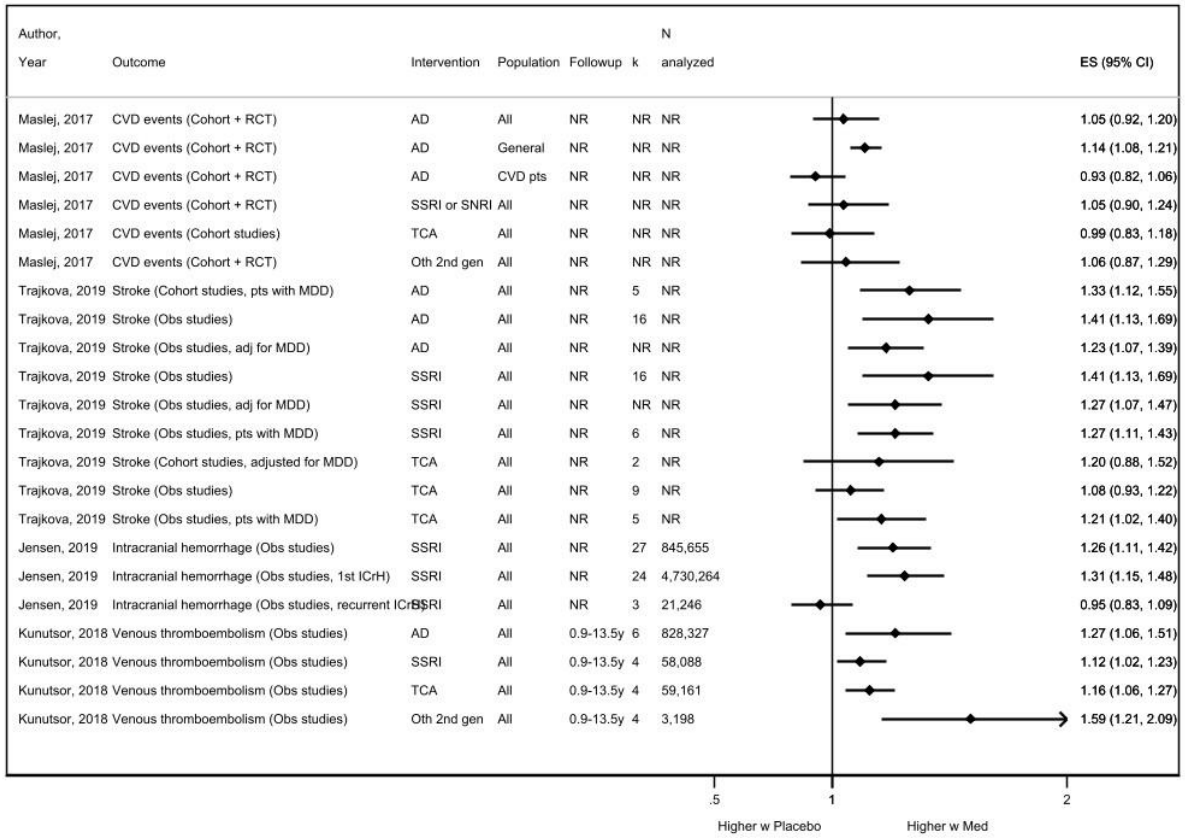
Abbreviations: CI = confidence interval; NR = not reported; RR = relative risk.

Figure 19. Forest Plot of Group Differences in Falls or Fractures With Pharmacological Treatment of Depression Compared to Placebo (KQ5)



Abbreviations: CI = confidence interval; ES = effect size; HR = hazard ratio; MDD = major depressive disorder; NR = not reported; RR = relative risk; SNRI = Serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Figure 20. Forest Plot of Group Differences in Cardiovascular-Related Outcomes With Pharmacological Treatment of Depression Compared to Placebo (KQ5)*

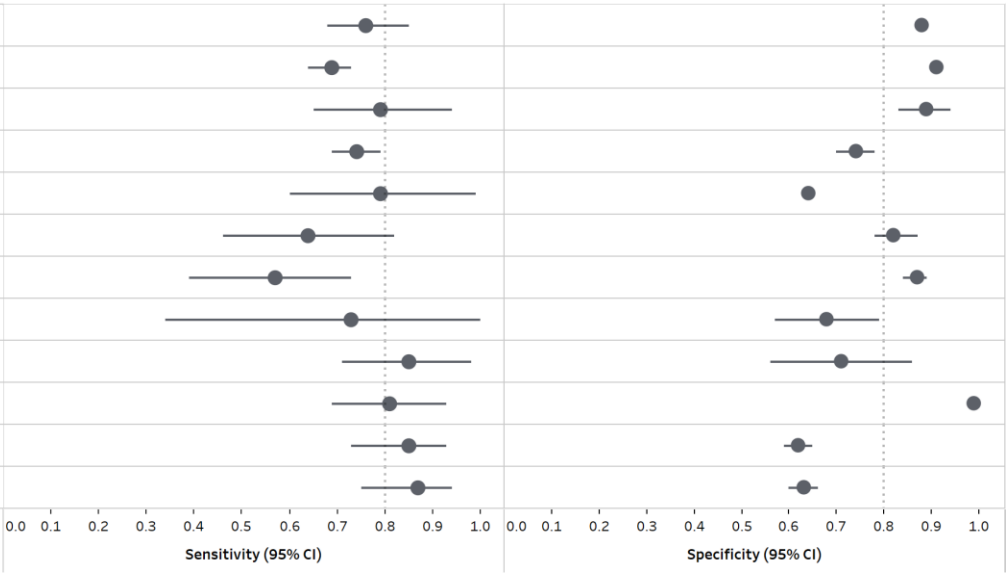


*Effects are RRs for all outcomes except those reported by Maslej, 2017, which are HRs.

Abbreviations: AD = antidepressant; CI = confidence interval; CVD = cardiovascular disease; ES = effect size; HR = hazard ratio; ICrH = intracranial hemorrhage; MDD = major depressive disorder; NR = not reported; RCT = randomized controlled trials; SNRI = Serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Figure 21. Summary of Test Accuracy of Screening Instruments to Detect Anxiety Disorders (KQ2)

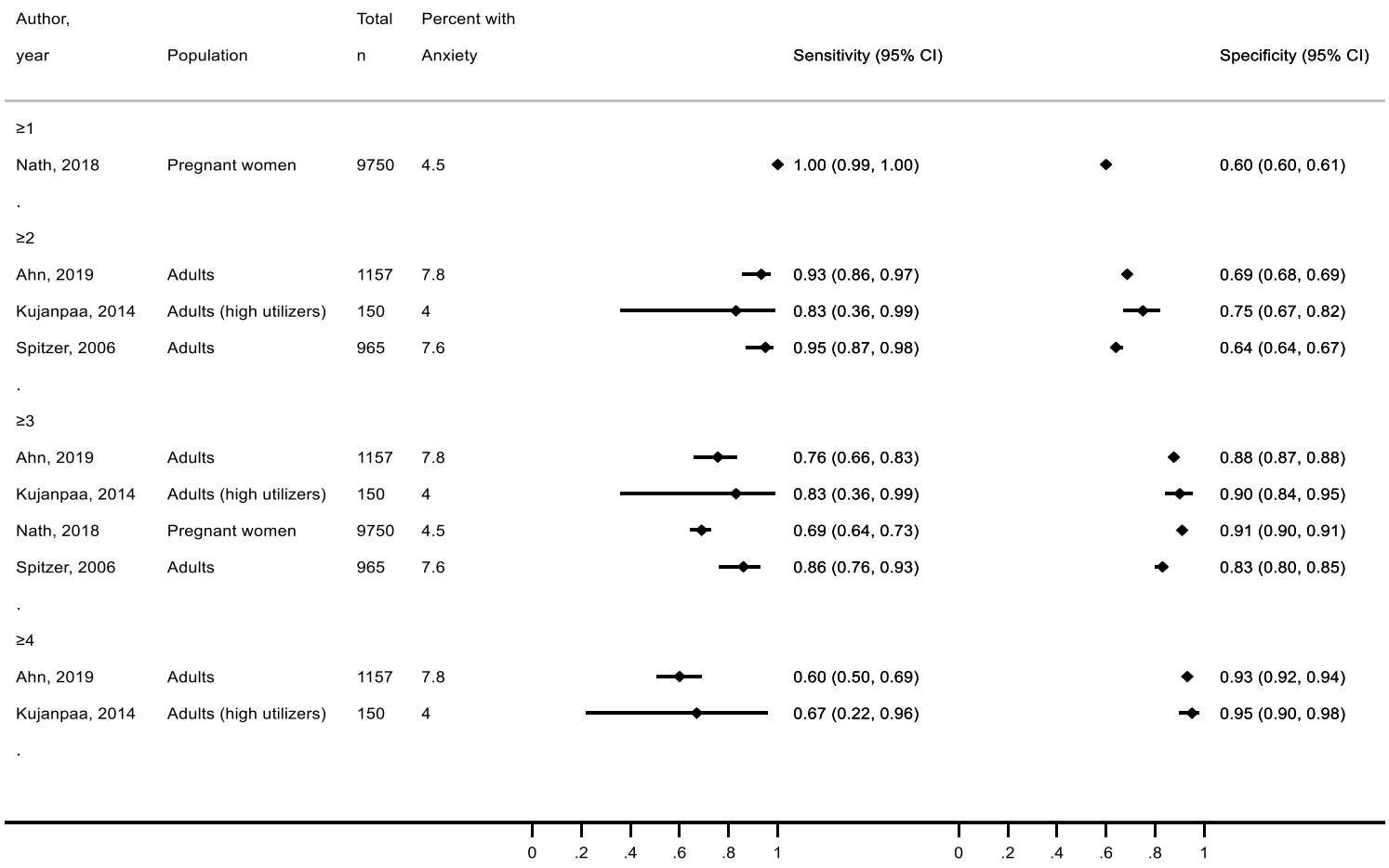
Condition	Screening Test	Population	No. of studies	No. of participants	Cutoff
Generalized Anxiety Disorder	GAD-2	Adults	2*	1,307	≥3
		Pregnant Women	1	9,750	≥3
	GAD-7	Adults	3	2,272	≥10
Any Anxiety Disorder	GAD-2	Adults	2*	1,307	≥2
		Pregnant Women	2*	10,474	≥1
	GAD-7	Adults	3	1,357	≥6
		Pregnant Women	1	954	≥6
Panic Disorder	GAD-2	Adults	2*	1,115	≥2
	GAD-7	Adults	2*	1,115	≥6
	PHQ-PD	Adults	1	585	5
Social Anxiety Disorder	GAD-2	Adults	1	965	≥2
	GAD-7	Adults	1	965	≥6



* Pooled results for fewer than 3 studies shown only for illustrative purposes.
Note: The number of participants for Generalized Anxiety Disorder and Any Anxiety Disorder, GAD-2, pregnant women are totaling with an extrapolated sample from one study.

Abbreviations: CI = Confidence interval; GAD = Generalized Anxiety Disorder.

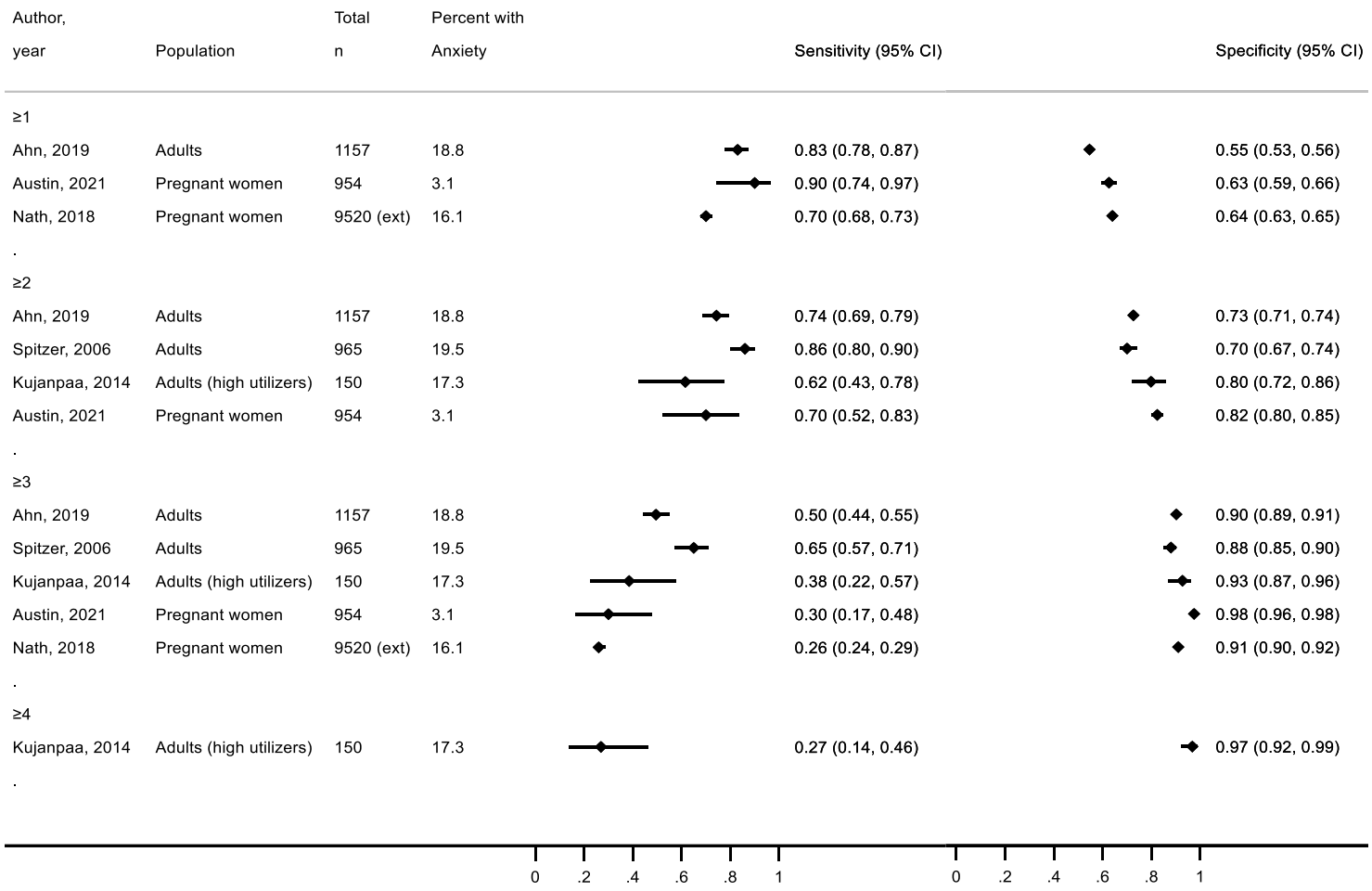
Figure 22. Test Accuracy of the GAD-2 to Detect Generalized Anxiety Disorder, by Cutoff (KQ2)



Note: Pooled results for the three general adult studies are not shown. At a cutoff of ≥2, pooled sensitivity was 0.94 (95% CI, 0.90 to 0.98; I^2=0%) and pooled specificity was 0.68 (95% CI, 0.64 to 0.72; I^2=94.5%). At a cutoff of ≥3, pooled sensitivity was 0.81 (95% CI, 0.73 to 0.89; I^2=28.8%) and pooled specificity was 0.86 (95% CI, 0.83 to 0.90; I^2=84.5%).

Abbreviations: CI = Confidence interval; GAD = Generalized Anxiety Disorder; n = number of participants.

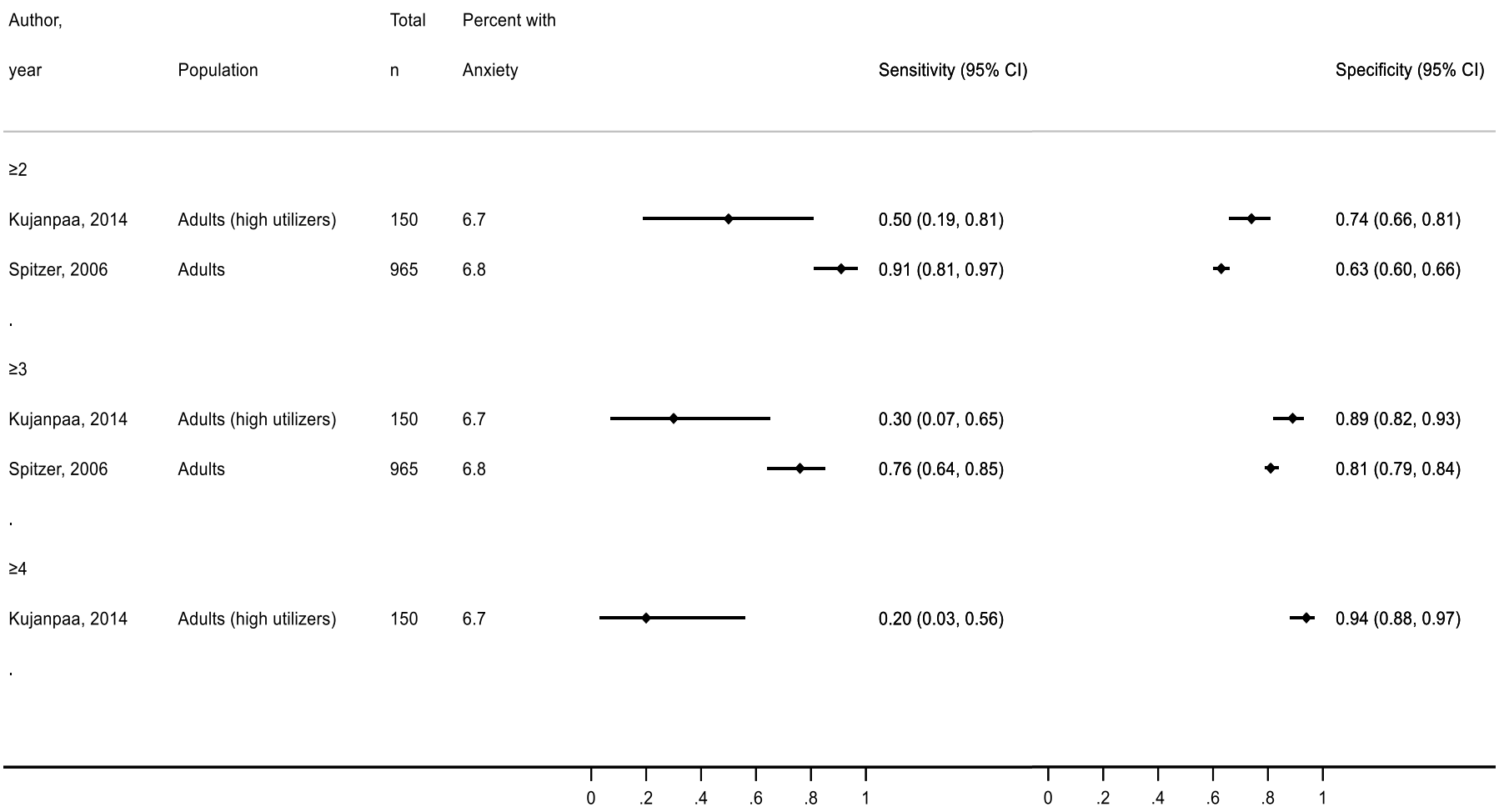
Figure 23. Test Accuracy of the GAD-2 to Detect Any Anxiety Disorder, by Cutoff (KQ2)



Note: Pooled results for the three general adult studies are not shown. At a cutoff of ≥2, pooled sensitivity was 0.76 (95% CI, 0.65 to 0.87; I^2=85.8%) and pooled specificity was 0.73 (95% CI, 0.69 to 0.76; I^2=67.7%). At a cutoff of ≥3, pooled sensitivity was 0.53 (95% CI, 0.39 to 0.66; I^2=86.8%) and pooled specificity was 0.90 (95% CI, 0.88 to 0.92; I^2=48.1%).

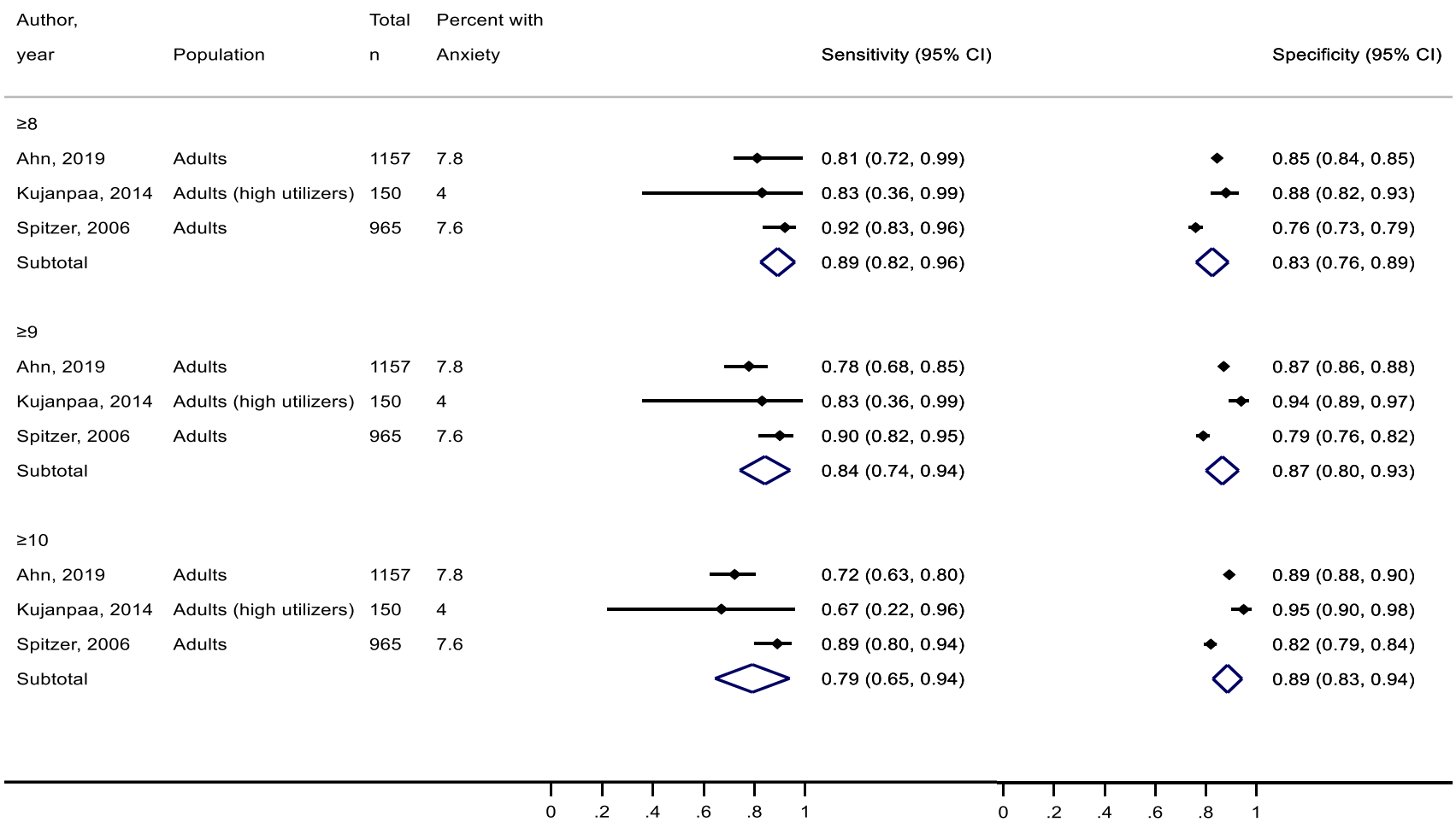
Abbreviations: CI = Confidence interval; ext = extrapolated; GAD = Generalized Anxiety Disorder; n = number of participants.

Figure 24. Test Accuracy of the GAD-2 to Detect Panic Disorder, by Cutoff (KQ2)



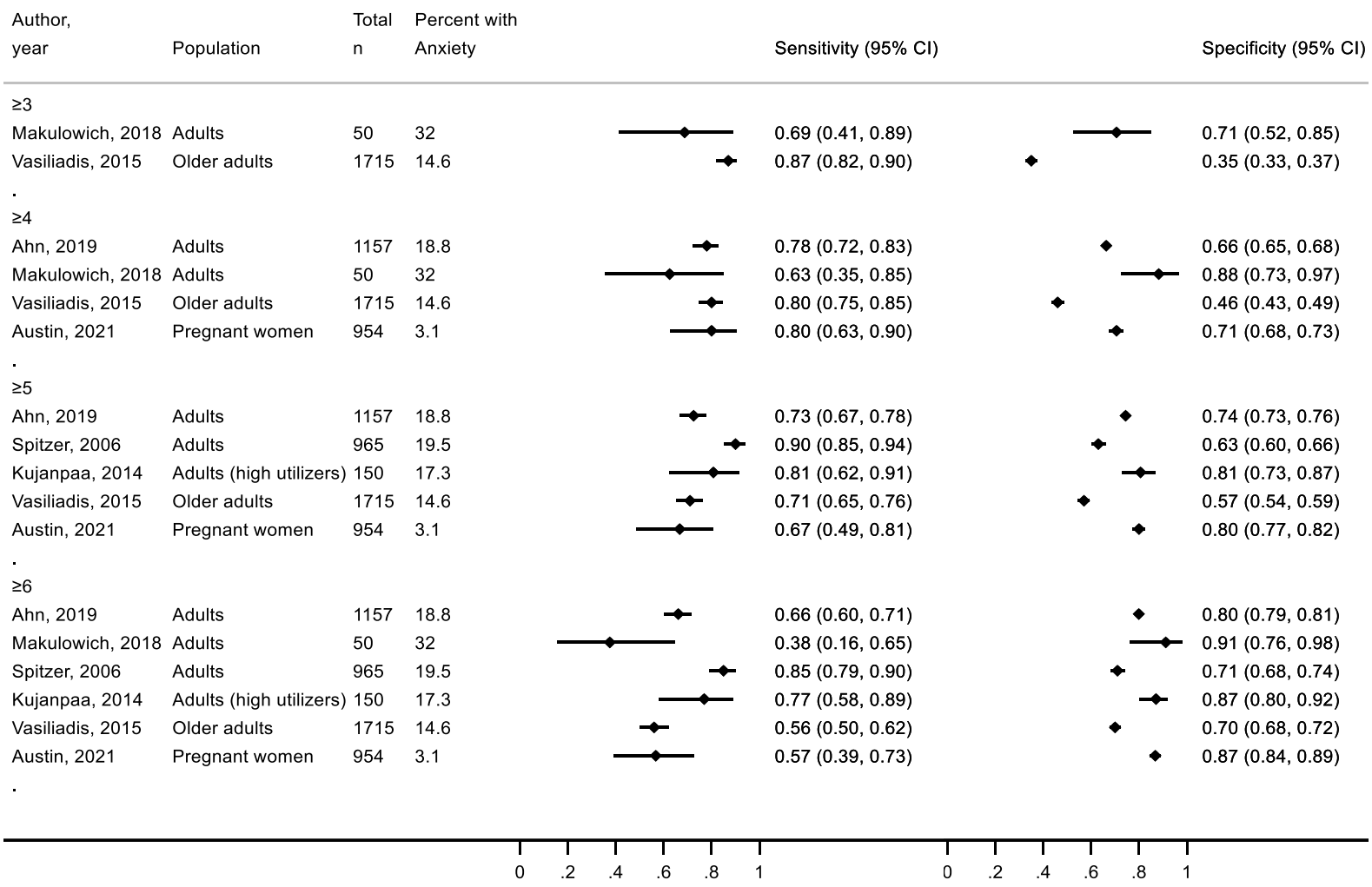
Abbreviations: CI = confidence interval; GAD = generalized anxiety disorder.

Figure 25. Test Accuracy of the GAD-7 to Detect Generalized Anxiety Disorder, by Cutoff (KQ2)



Abbreviations: CI = Confidence interval; GAD = Generalized Anxiety Disorder; n = number of participants.

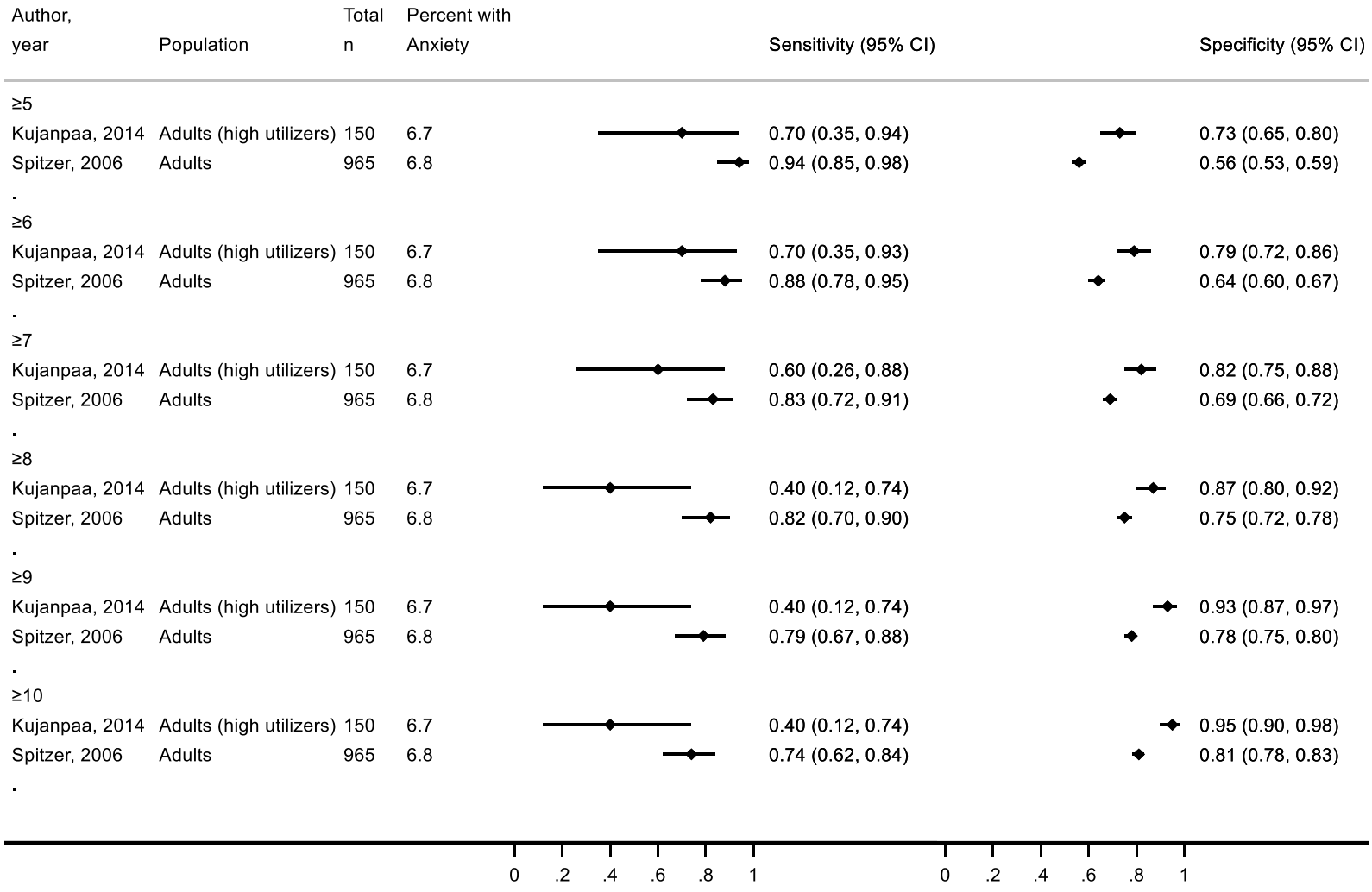
Figure 26. Test Accuracy of the GAD-7 to Detect Any Anxiety Disorder, by Cutoff (KQ2)



Note: Pooled results for the four general adult studies are not shown. At a cutoff of ≥6, pooled sensitivity was 0.67 (95% CI, 0.48 to 0.81; I^2=90.5%) and pooled specificity was 0.81 (95% CI, 0.73 to 0.87; I^2=91.0%). At a cutoff of ≥5, pooled sensitivity was 0.81 (95% CI, 0.68 to 0.95; I^2=91.4%) and pooled specificity was 0.72 (95% CI, 0.63 to 0.81; I^2=96.1%) (k=3).

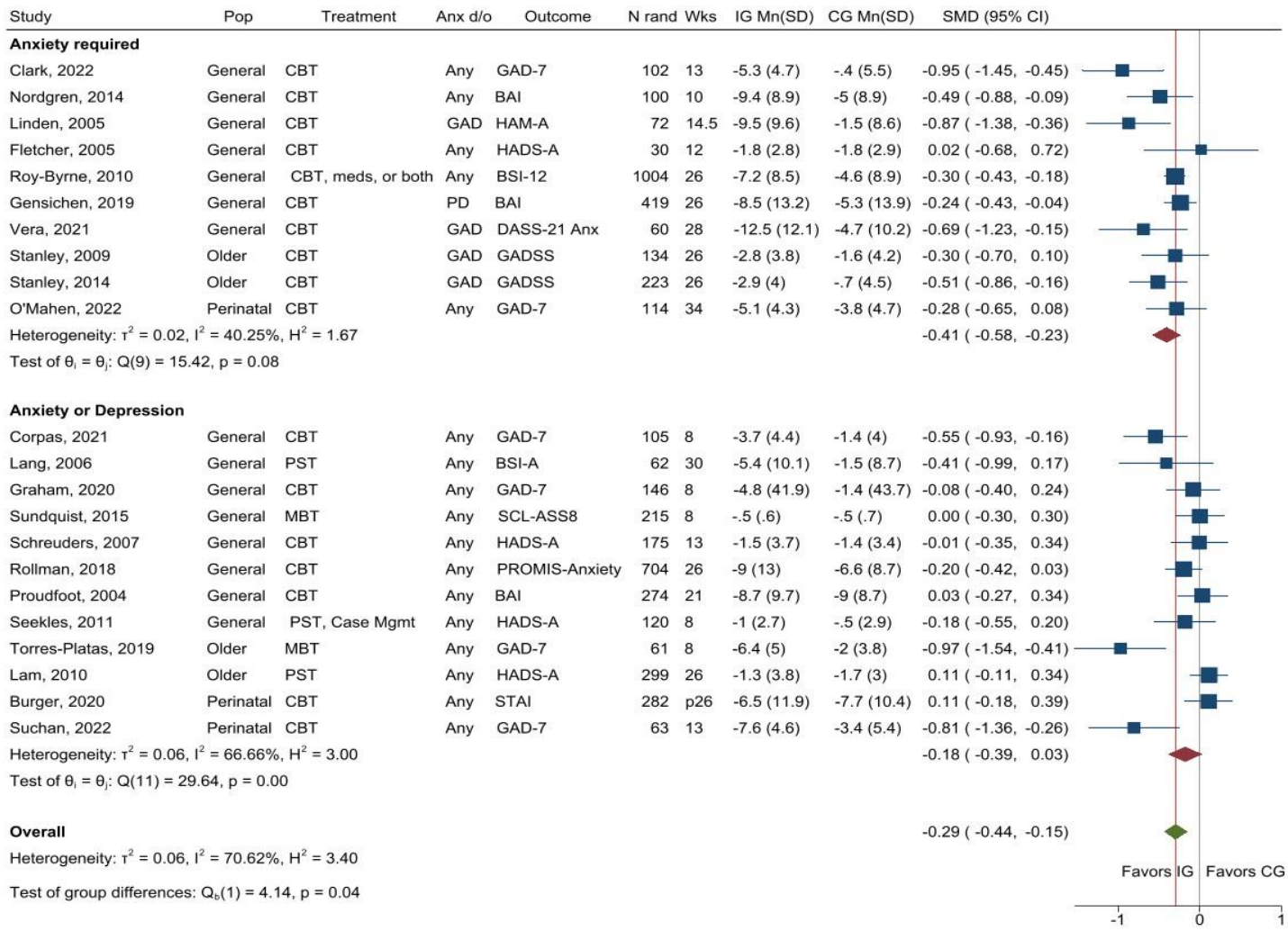
Abbreviations: CI = confidence interval; GAD = Generalized Anxiety Disorder; n = number of participants.

Figure 27. Test Accuracy of the GAD-7 to Detect Panic Disorder, by Cutoff (KQ2)



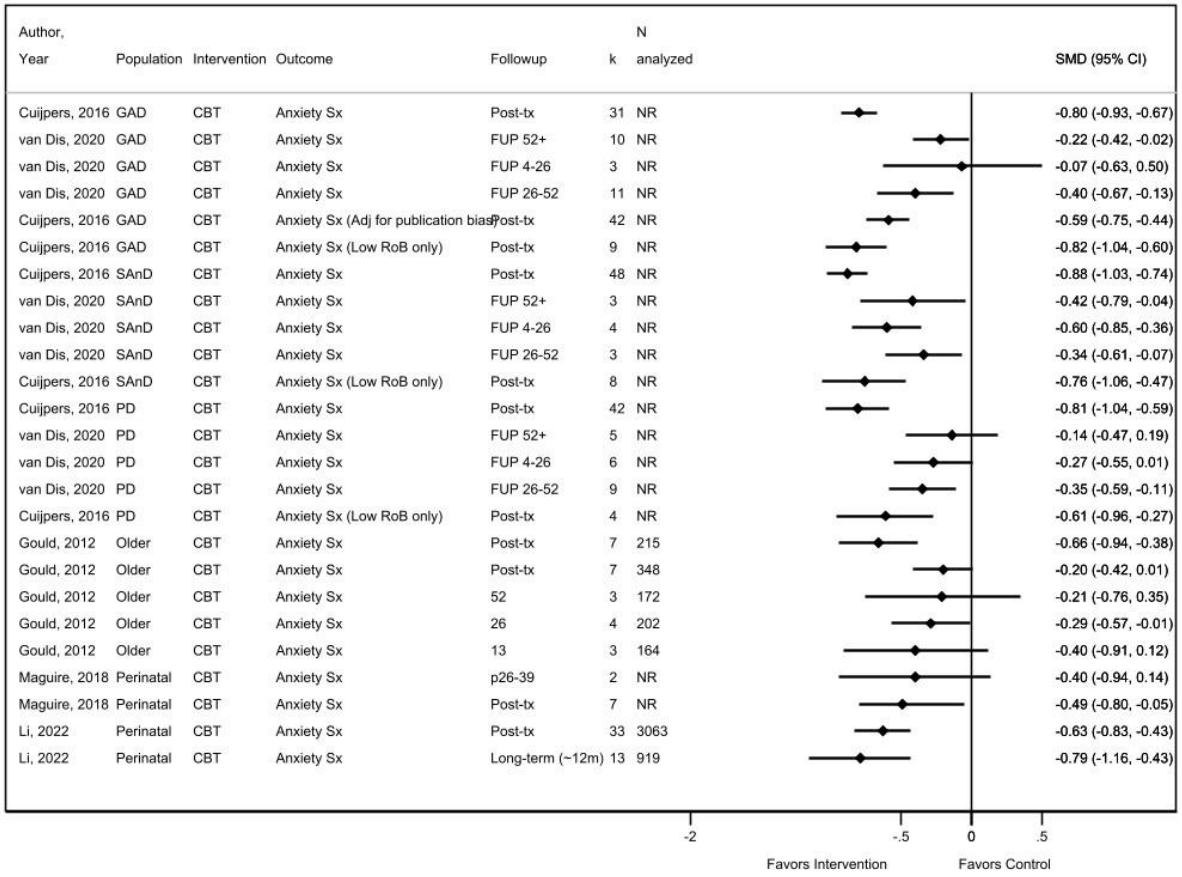
Abbreviations: CI = confidence interval; GAD = Generalized Anxiety Disorder.

Figure 28. Forest Plot Showing the Difference Between Groups in Change From Baseline in Anxiety Symptoms, for Primary Studies of Psychological Intervention for Treatment of Anxiety in Primary Care Populations Reported in Primary RCTs (KQ4)



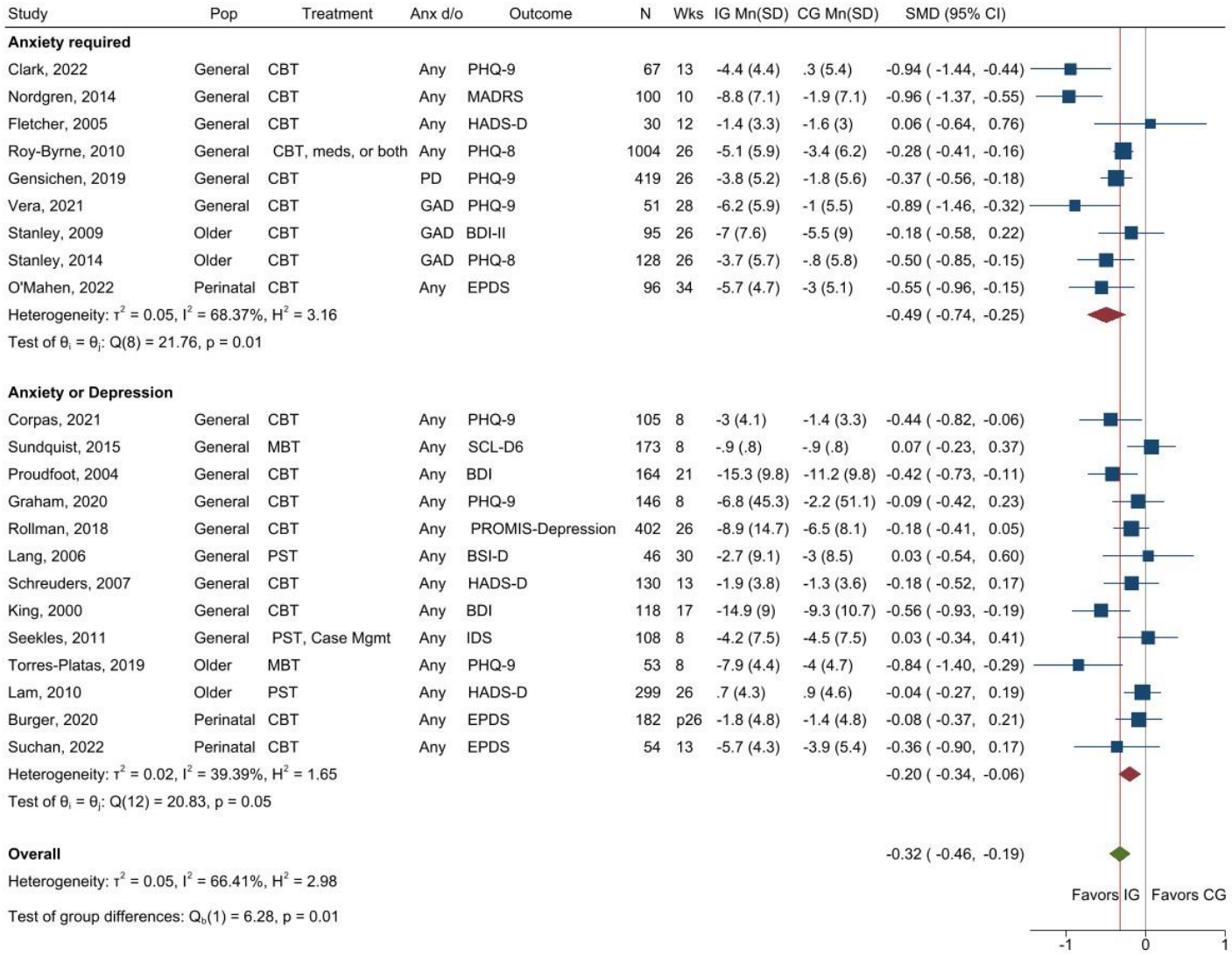
Abbreviations: BAI = Beck Anxiety Inventory; BSI = Brief Symptom Inventory; CBT = cognitive behavioral therapy; CG = control group; GAD = generalized anxiety disorder; GADSS = Generalized Anxiety Disorder Severity Scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety; Hamilton Anxiety Rating Scale; IG = intervention group; MBT mindfulness-based therapy; PROMIS – Anxiety = Patient-Reported Outcomes Measurement Information System – Anxiety; PST = problem solving therapy; SCL-ASS8 = Symptom Checklist – Anxiety Symptom Scale; SD = standard deviation; SMD = standardized mean difference; STAI = State Trait Anxiety Inventory.

Figure 29. Forest Plot of Standardized Mean Differences Between Groups in Anxiety Symptom Severity for Psychological Treatment of Anxiety Compared to Controls Reported in ESRs (KQ4)



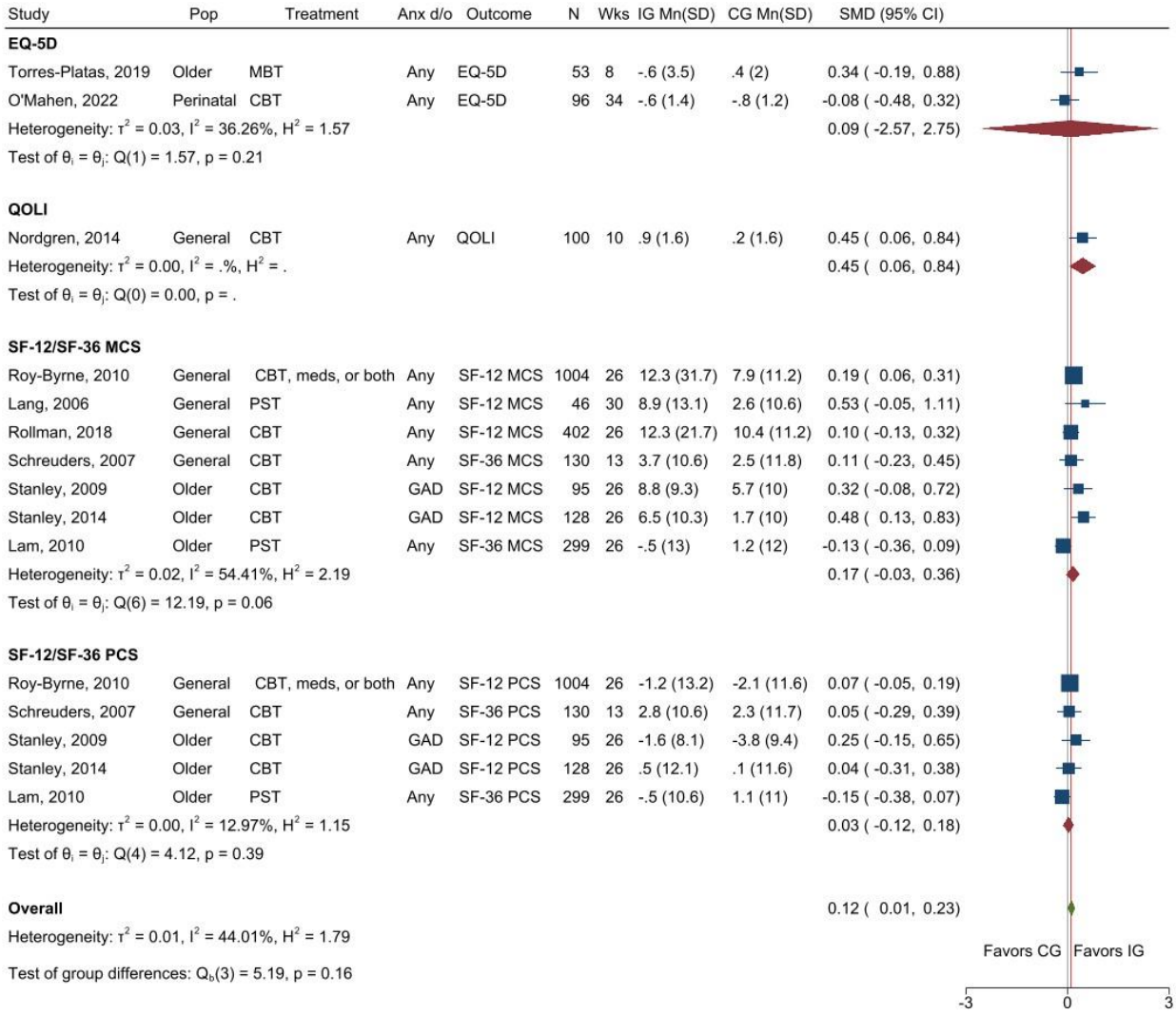
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; FUP = followup; GAD = generalized anxiety disorder; NR = not reported; RoB = risk of bias; PD = panic disorder; SaND = social anxiety disorder; SMD = standardized mean difference.

Figure 30. Forest Plot Showing the Difference Between Groups in Change From Baseline in Depression Symptoms, for Primary Studies of Psychological Intervention for Treatment of Anxiety in Primary Care Populations (KQ4)



Abbreviations: BDI = Beck Depression Inventory; BSI = Brief Symptom Inventory; CBT = cognitive behavioral therapy; CG = control group; EPDS = Edinburgh Postnatal Depression Scale; GAD = Generalized Anxiety Disorder; HADS-D = Hospital Anxiety and Depression Scale – Depression; IDS = Inventory of Depressive Symptomatology; IG = intervention group; MBT = mindfulness-based therapy; p26 = Assessment at 26 weeks postpartum; PHQ = Patient Health Questionnaire; PROMIS – Depression = Patient-Reported Outcomes Measurement Information System – Depression; PST = problem solving therapy; SCL-D6 = Symptom Checklist – Core Depression; SD = standard deviation; SMD = standardized mean difference.

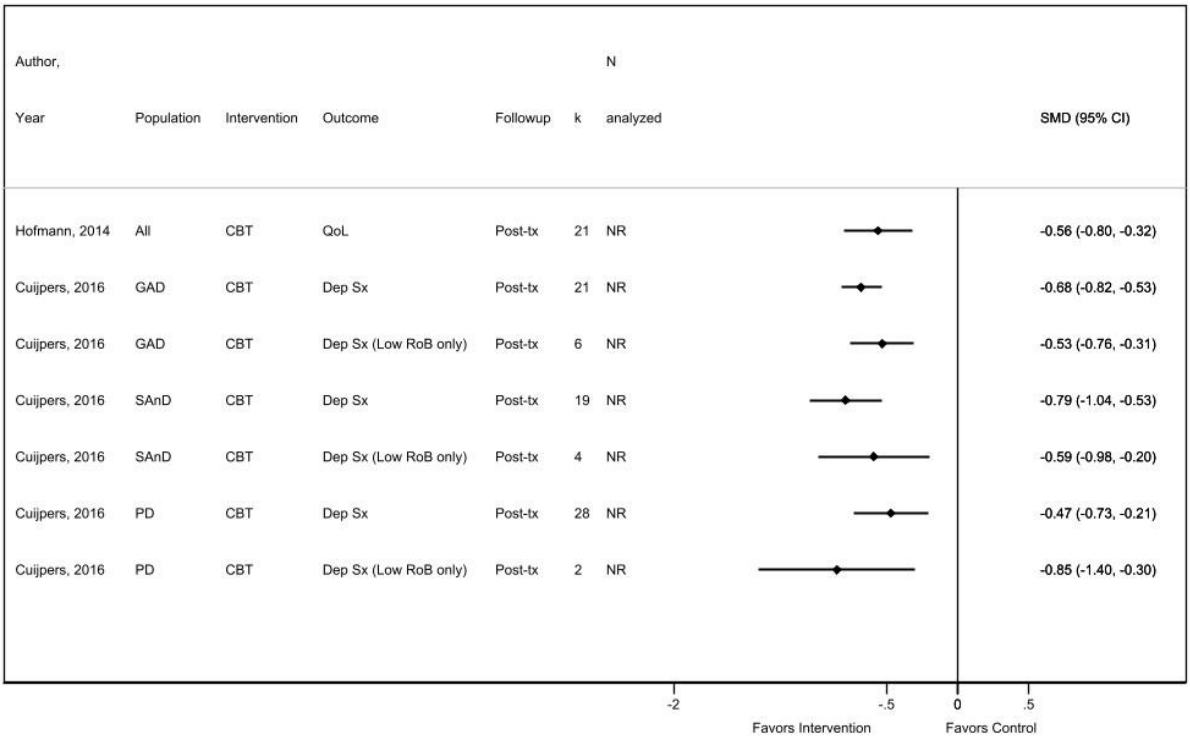
Figure 31. Forest Plot Showing the Difference Between Groups in Change From Baseline in Quality of Life Measures, for Primary Studies of Psychological Intervention for Treatment of Anxiety in Primary Care Populations (KQ4)*



*For the EQ-5D, a higher score indicates a worse outcome (unlike all other QoL outcomes shown), so the effect for EQ-5D is in the direction of benefit.

Abbreviations: CBT = cognitive behavioral therapy; CG = control group; EQ-5D = EuroQol-5D; GAD = generalized anxiety disorder; QOLI = Quality of Life Inventory; MBT mindfulness-based therapy; MCS = Mental Component Score; SF = Short Form; PCS = Physical Component Score; PST = problem solving therapy.

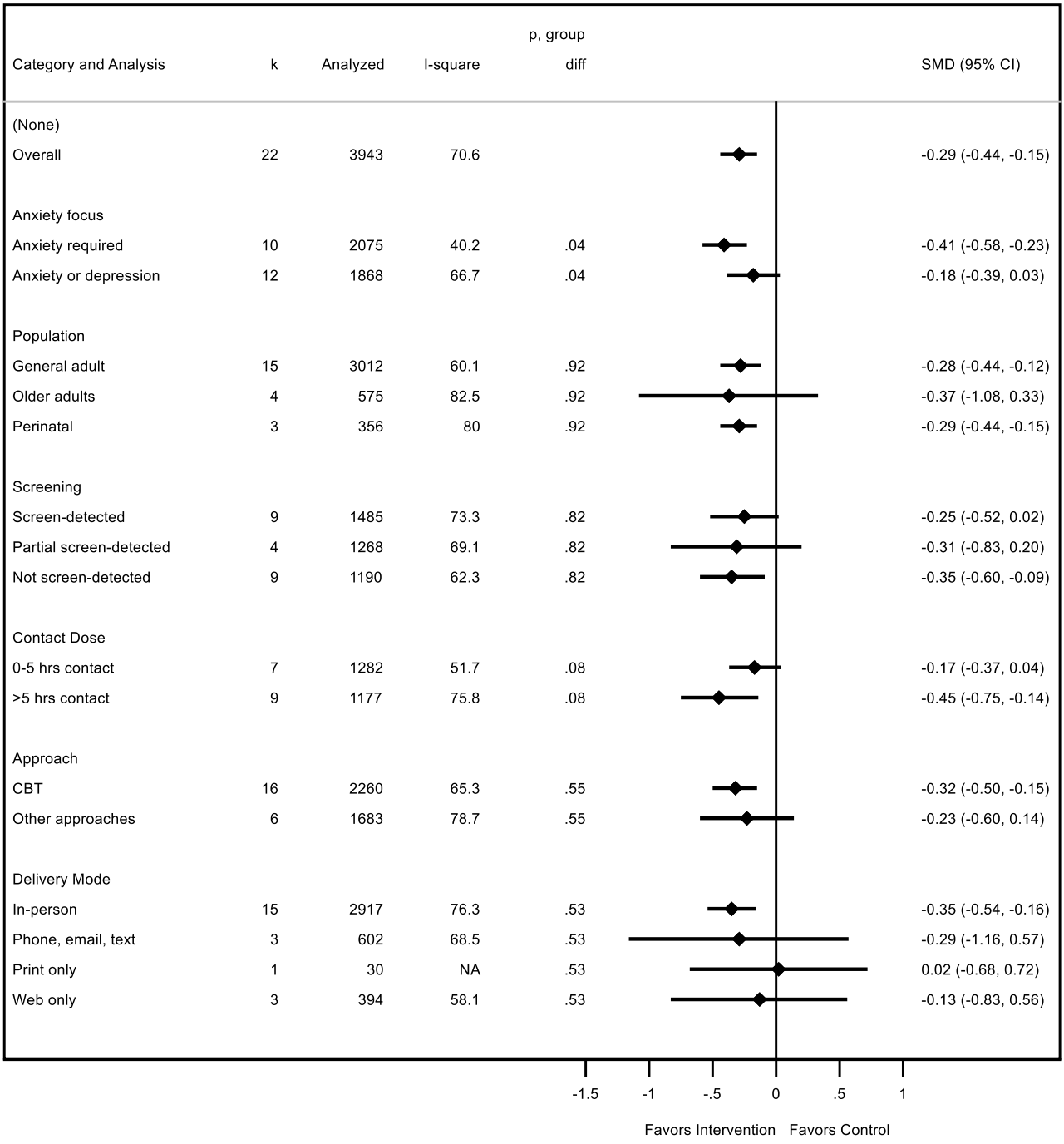
Figure 32. Forest Plot of Standardized Mean Differences Between Groups in Other Outcomes for Psychological Treatment of Anxiety Compared to Controls (KQ4)*



*For the EQ-5D, a higher score indicates a worse outcome (unlike all other QoL outcomes shown), so the effect for EQ-5D is in the direction of benefit.

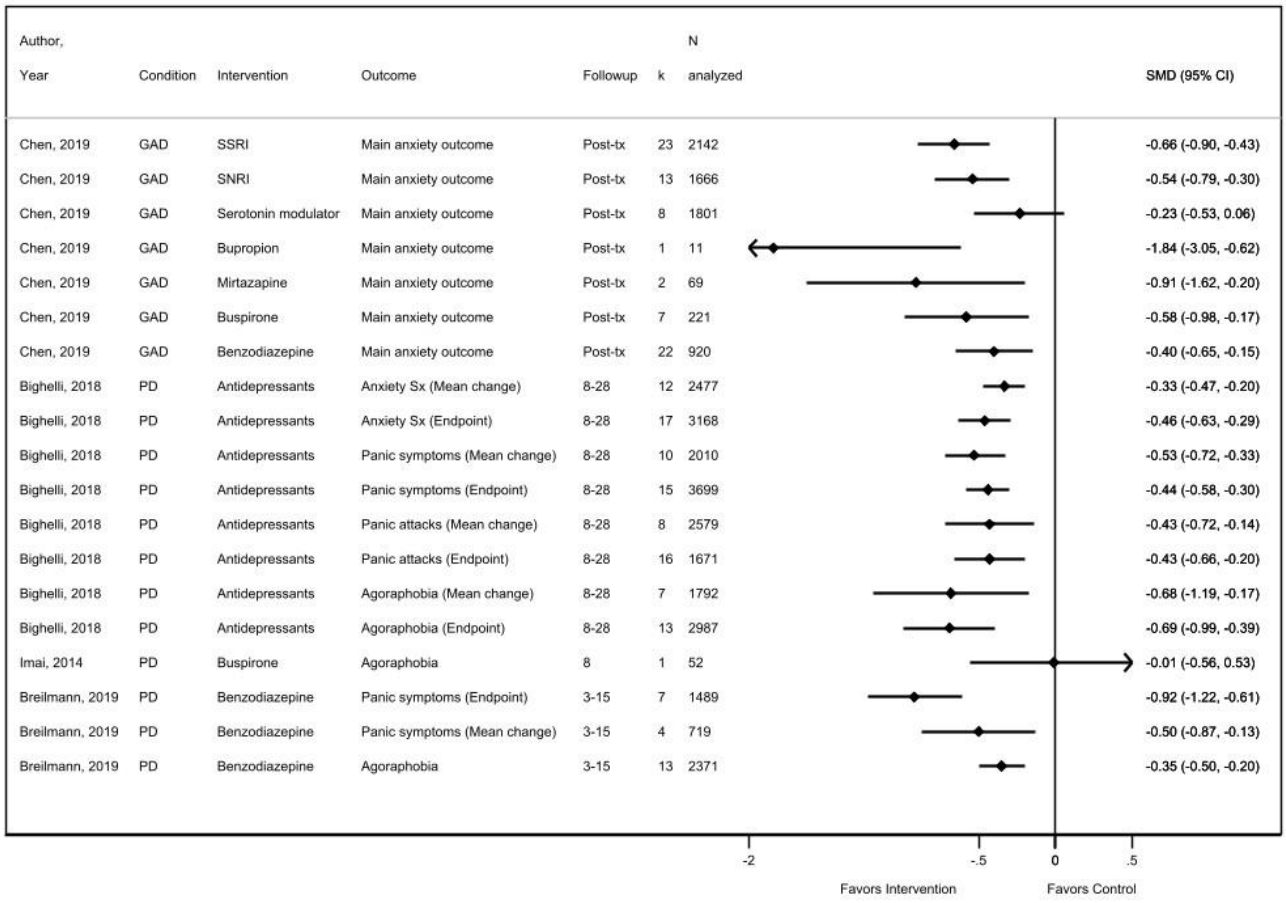
Abbreviations: CBT = cognitive behavioral therapy; GAD = generalized anxiety disorder; QoL = Quality of Life; NR = not reported; PD = panic disorder; SaND = social anxiety disorder; SMD = standardized mean difference.

Figure 33. Stratified Analyses Examining Effect Modification for Anxiety Symptom Severity in Primary Studies of Anxiety Treatment Among Primary Care Patients (KQ4)



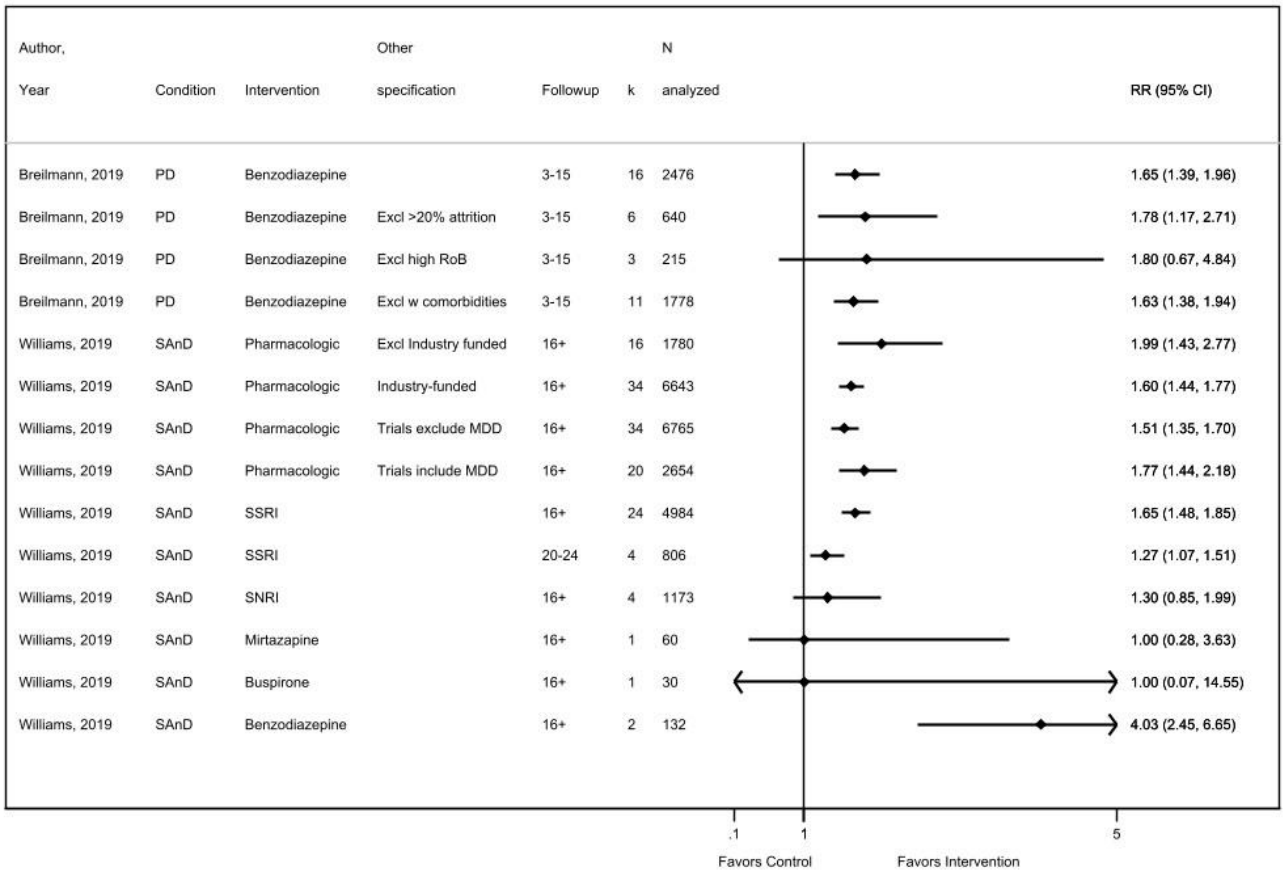
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; NA = not applicable; SMD = standardized mean difference.

Figure 34. Forest Plot of Standardized Mean Differences Between Groups in Anxiety Symptom Severity for Pharmacologic Treatment of Anxiety Compared to Controls (KQ4)



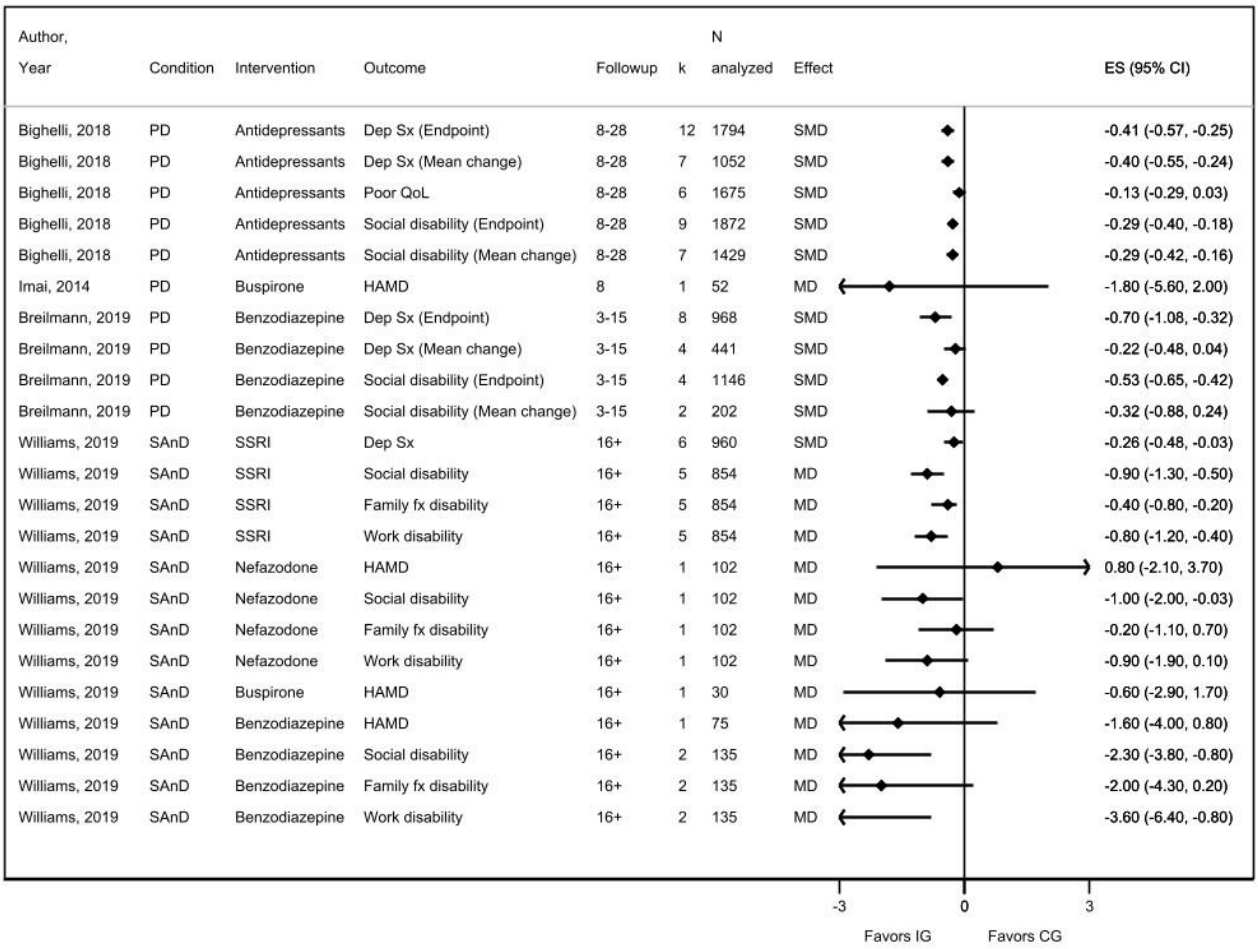
Abbreviations: CI = confidence interval; GAD = generalized anxiety disorder; PD = panic disorder; SMD = standardized mean difference; SNRI = Serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Figure 35. Forest Plot of Odds Ratios for Group Differences in the Odds of Treatment Response With Pharmacological Treatment of Anxiety Compared to Placebo (KQ4)



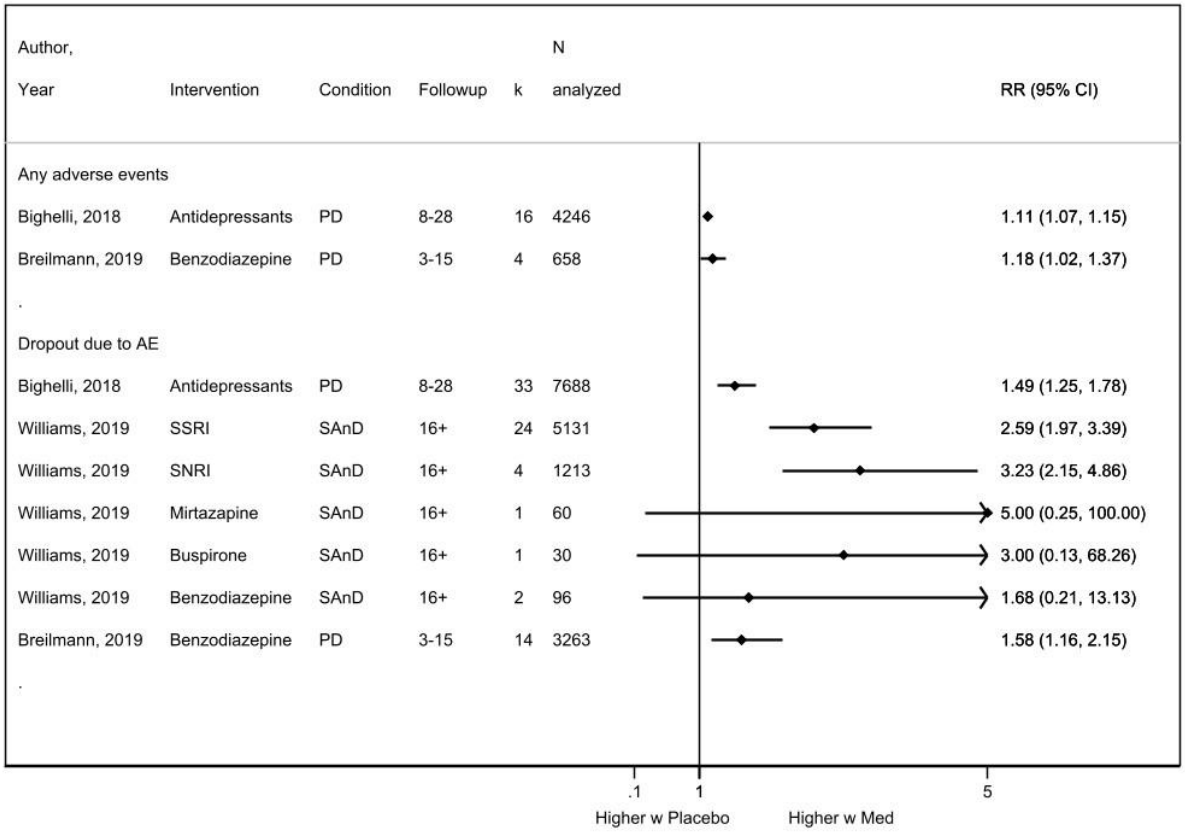
Abbreviations: CI = confidence interval; GAD = generalized anxiety disorder; MDD = major depressive disorder; PD = panic disorder; RoB = risk of bias; RR = relative risk; SaND = social anxiety disorder; SNRI = Serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Figure 36. Forest Plot of Groups in Other Outcomes for Pharmacologic Treatment of Anxiety Compared to Placebo (KQ4)



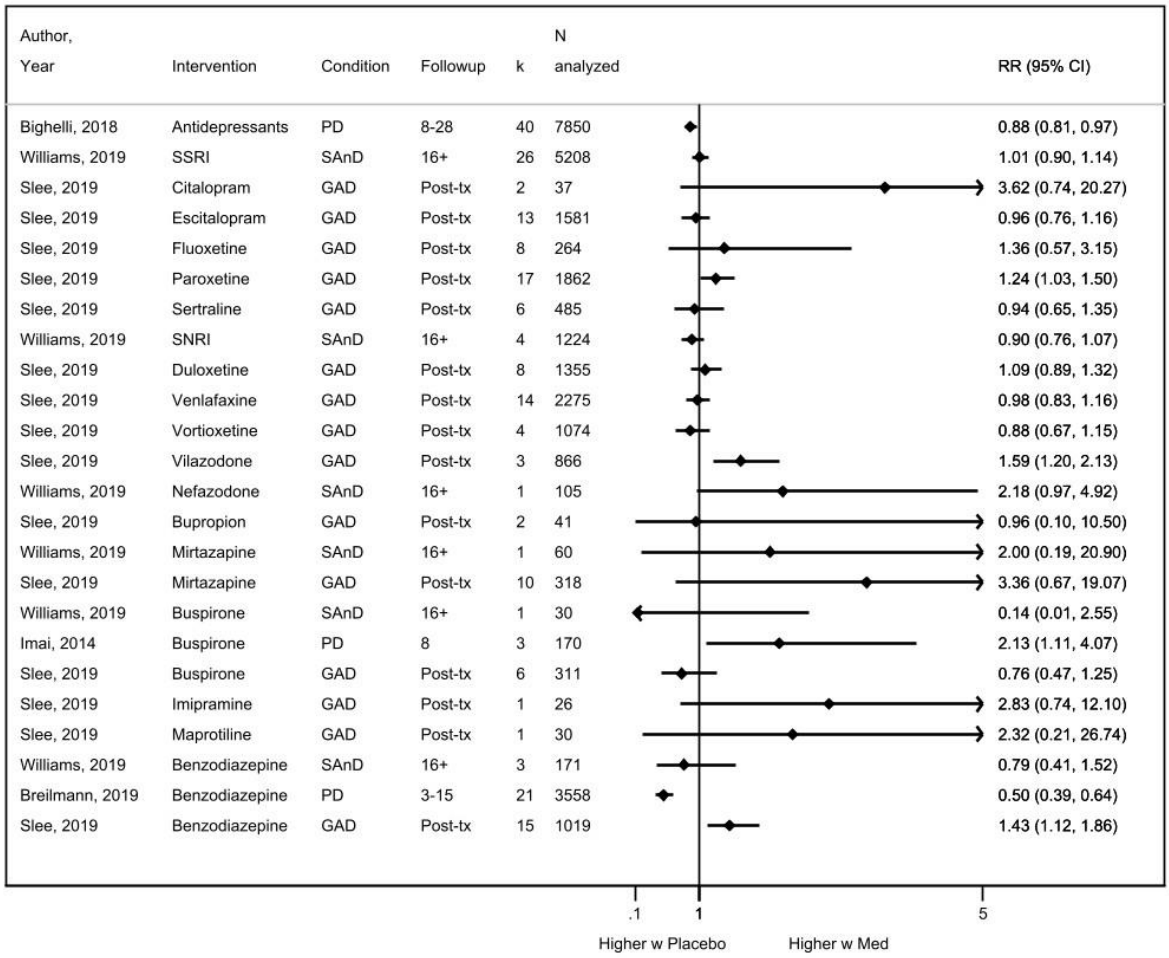
Abbreviations: CG = control group; CI = confidence interval; ES = effect size; HAMD = Hamilton Rating Scale for Depression; IG = intervention group; MD = mean difference; MDD = major depressive disorder; PD = panic disorder; QoL = quality of life; SaND = social anxiety disorder; SNRI = Serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Figure 37. Forest Plot of Group Differences in Dropout Due to Adverse Events in ESRs With Pharmacological Treatment of Anxiety Compared to Placebo (KQ5)



Abbreviations: AE = adverse event; CI = confidence interval; PD = panic disorder; RR = relative risk; SaND = social anxiety disorder; SNRI = Serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

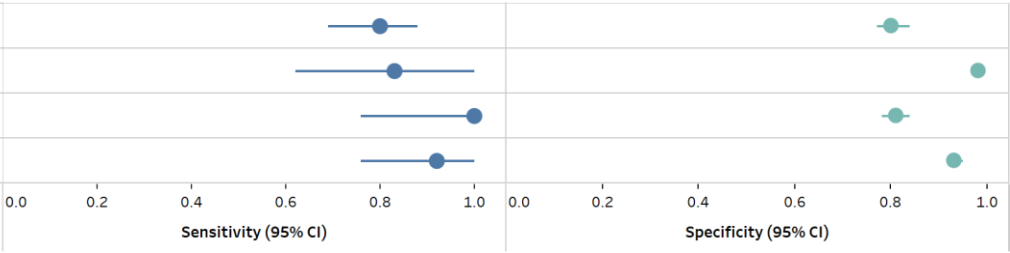
Figure 38. Forest Plot of Group Differences in Dropout for Any Reason in ESRs With Pharmacological Treatment of Anxiety Compared to Placebo (KQ5)



Abbreviations: CI = confidence interval; GAD = generalized anxiety disorder; PD = panic disorder; RR = relative risk; SaND = social anxiety disorder; SNRI = Serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

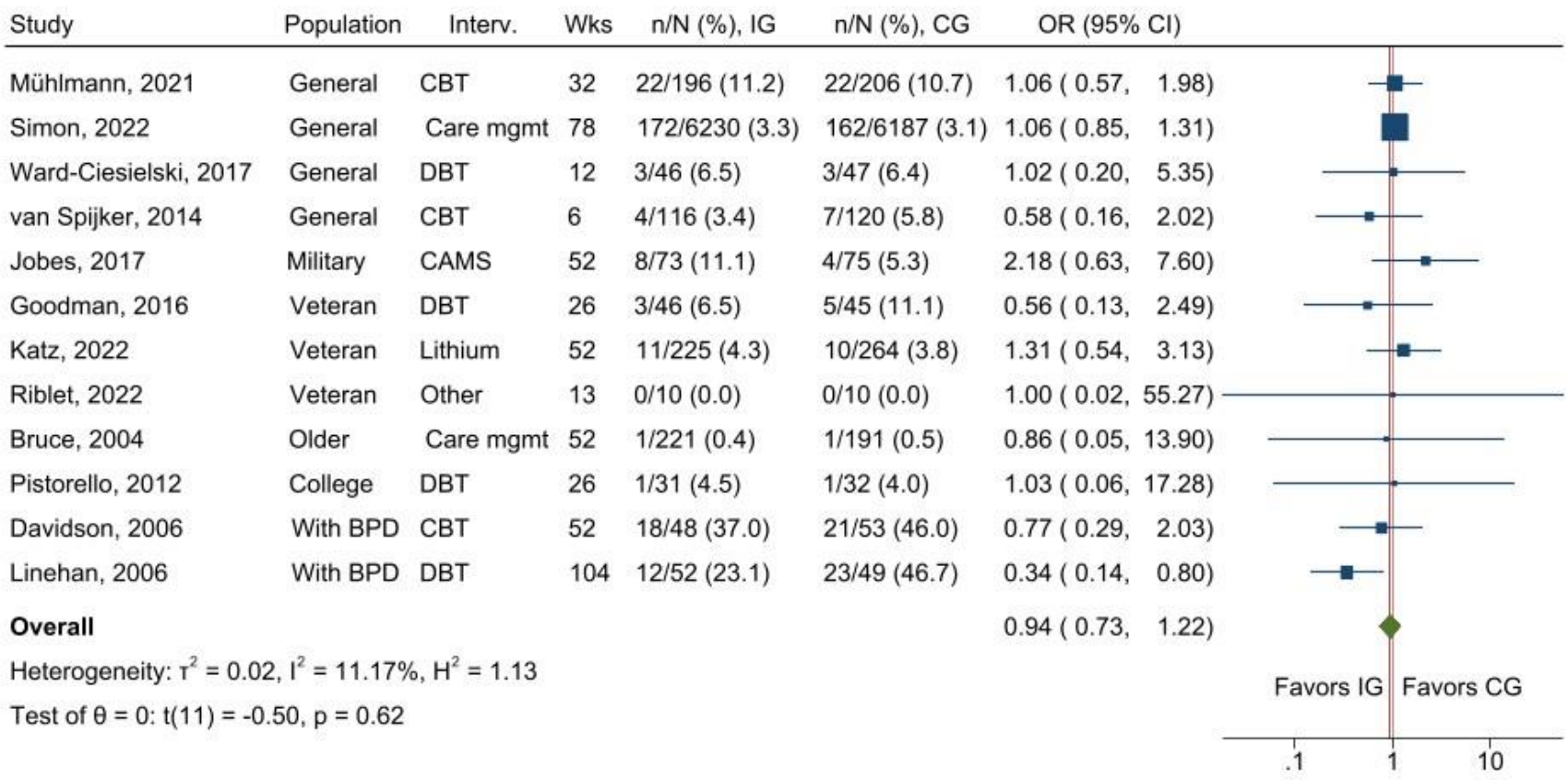
Figure 39. Summary of Test Accuracy of Screening Tools to Detect High Risk of Suicide (KQ2)

Condition	Screening Test	Population	No. of studies	No. of participants	Cutoff
Suicidal Ideation	GDS-SI	Older Adults	1	626	≥1
	SDDS-PC Feeling Suicidal	Adults	1	1,001	NA
	SDDS-PC Thoughts of Death	Adults	1	1,001	NA
	SDDS-PC Wishing You Were Dead	Adults	1	1,001	NA



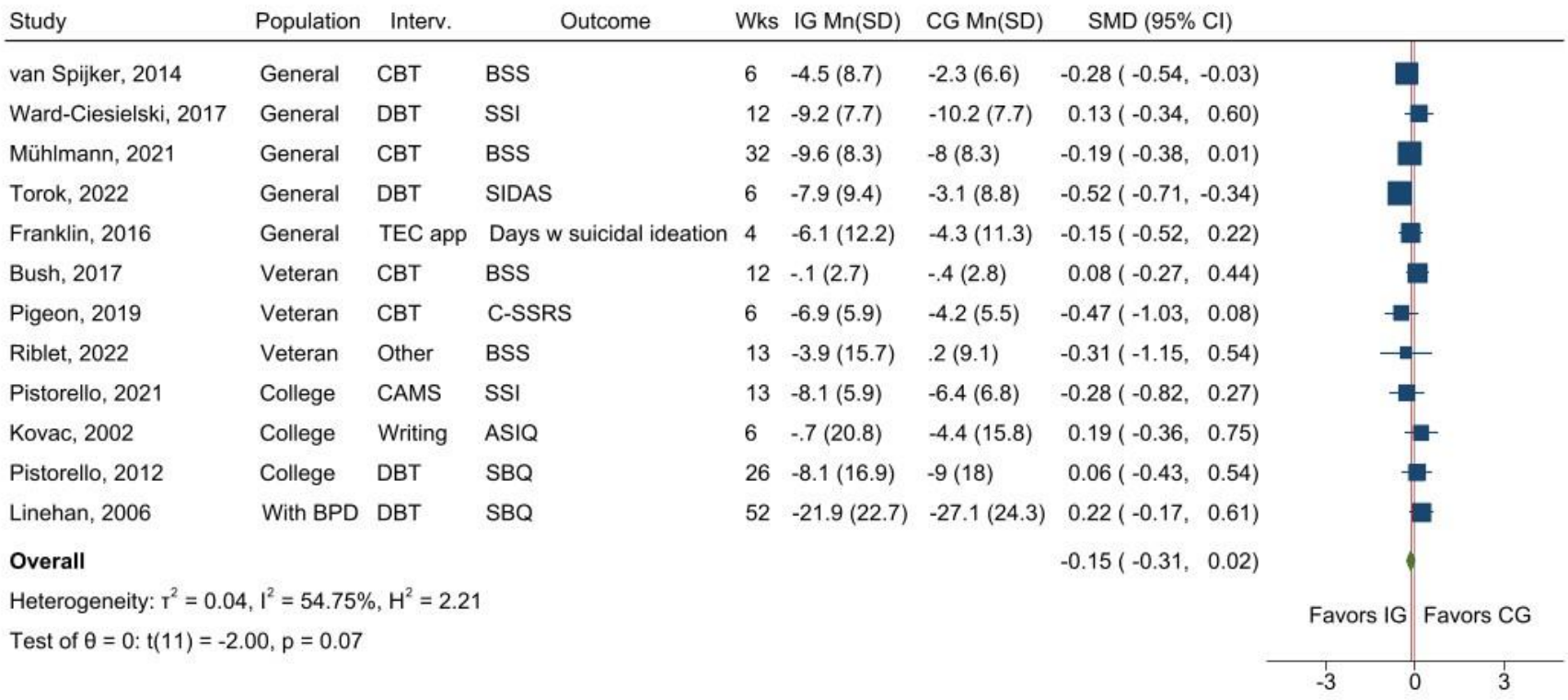
Abbreviations: CI = Confidence interval; GDS-SI = Geriatric Depression Scale – Suicide Ideation; NA = Not applicable; SDDS-PC = Symptom Driven Diagnostic System for Primary Care.

Figure 40. Forest Plot of Proportion With a Suicide Attempt From the Suicide Prevention Trials (KQ4)



Abbreviations: BPD = bipolar disorder; CAMS = Collaborative Assessment and Management of Suicidality; CBT = cognitive behavioral therapy; CG = control group; CI = Confidence interval; DBT = dialectical behavioral therapy; GDS-SI = Geriatric Depression Scale – Suicide Ideation; IG = intervention group; NA = Not applicable; OR = odds ratio; SDDS-PC = Symptom Driven Diagnostic System for Primary Care.

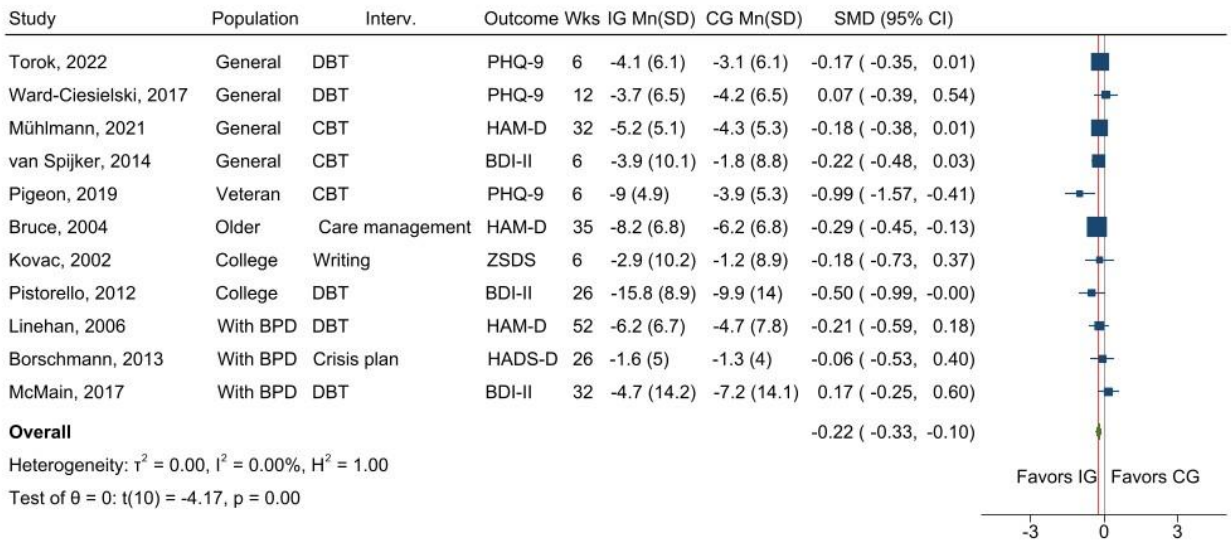
Figure 41. Forest Plot of Standardized Mean Difference in Change From Baseline of Continuous Suicidal Ideation Measures From the Suicide Prevention Trials (KQ4)



Note: "IG/CG Mn(SD)" show change from baseline in the native units of the measures reported.

Abbreviations: ASIQ = Adult Suicidal Ideation Questionnaire; BPD = bipolar disorder; BSS = Beck Scale for Suicide ideation; CBT = cognitive behavioral therapy; CG = control group; CI = Confidence interval; C-SRRS = Columbia-Suicide Severity Rating Scale; DBT = dialectical behavioral therapy; IG = intervention group; SBQ = Suicide Behaviors Questionnaire; SD = standard deviation; SMD = standardized mean difference; SSI = Scale for Suicidal Ideation.

Figure 42. Forest Plot of Depression Symptom Severity Scores From the Suicide Prevention Trials (KQ4)



Note: "IG/CG Mn(SD)" show change from baseline in the native units of the measures reported.

Abbreviations: BDI = Beck Depression Inventory; BPD = bipolar disorder; CBT = cognitive behavioral therapy; CG = control group; CI = Confidence interval; DBT = dialectical behavioral therapy; HADS-D = Hospital Anxiety and Depression Scale – Depression; HAM-D = Hamilton Rating Scale for Depression; IG = intervention group; PHQ = Patient Health Questionnaire; SD = standard deviation; SMD = standardized mean difference; ZSDS = Zung Self-rating Depression Scale.

Table 1. Percent of U.S. Adults With a Major Depressive Episode in the Past Year, 2019

Category	Total (2019)	Male (2019)	Female (2019)
Total	7.8	6.0	9.6
Age, yrs			
18-25	15.2	11.1	19.4
26-49	8.9	6.6	11.1
50 or Older	4.7	3.8	5.6
65 or Older	3.3	3.0	3.5
Hispanic origin and race			
Not Hispanic or Latino	8.0	NR	NR
White	8.5	NR	NR
Black or African American	6.3	NR	NR
American Indian or Alaska Native	9.4	NR	NR
Native Hawaiian or Pacific Islander	3.5	NR	NR
Asian American	4.7	NR	NR
Two or more races	13.7	NR	NR
Hispanic or Latino	6.8	NR	NR

Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug and Health, 2019.[455]

Abbreviation: NR = not reported.

Table 2. 12-Month Prevalence of DSM-IV/WMH-CIDI Disorders by Sex and Cohort (n=9,282)[456]

Demographic characteristic	Any anxiety disorder, %	Panic disorder	Generalized anxiety disorder	Social phobia*
Total	19.1	2.7	2.7	7.1
Gender				
Male	14.3	1.6	1.9	6.1
Female	23.4	3.8	3.4	8.0
Age				
18-29	22.3	2.8	2.0	9.1
30-44	22.7	3.7	3.5	8.7
45-59	20.6	3.1	3.4	6.8
60+	9.0	0.8	1.5	3.1

*Social phobia was the term used at the time of the original survey and was replaced by the term "Social Anxiety Disorder."

Abbreviations: DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; WMH-CIDI = World Health Organization World Mental Health Composite International Diagnostic Interview.

Table 3. Annual Number and Age-Adjusted* Rate of Suicide† per 100,000 Population, National Vital Statistics System, United States, 2019[37]

Demographic characteristic	Total no. (rate)	Male no. (rate)	Female no. (rate)
Total	47,511 (13.9)	37,256 (22.4)	10,255 (6.0)
Age group, yrs			
10-14	534 (2.6)	331 (3.1)	203 (2.0)
15-24	5,954 (14.0)	4,800 (22.0)	1,154 (5.5)
25-34	8,059 (17.5)	6,533 (28.0)	1,526 (6.8)
35-44	7,525 (18.1)	5,815 (28.0)	1,526 (6.8)
45-54	8,012 (19.6)	5,856 (29.0)	2,156 (10.4)
55-64	8,238 (19.4)	6,290 (30.7)	1,948 (8.9)
65-74	4,867 (15.5)	3,882 (26.4	985 (5.9)
75-84	2,977 (18.6)	2,567 (36.7)	410 (4.6)
≥85	1,329 (20.1)	1,171 (49.3)	158 (3.7)
Hispanic origin and race			
White	37,428 (17.7)	29,382 (28.1)	8,046 (7.7)
Black or African American	3,115 (7.5)	2,491 (12.5)	624 (2.9)
American Indian/Alaska Native	546 (22.5)	401 (33.0)	145 (12.1)
Native Hawaiian/Pacific Islander	90 (14.4)	72 (22.1)	18 (-)
Asian	1,342 (6.7)	950 (10.1)	392 (3.7)
Multiracial	527 (8.8)	405 (14.2)	122 (3.9)
Hispanic	4,331 (7.3)	3,445 (11.6)	886 (3.0)
Unknown	132 (-)	110 (-)	22 (-)

Table 4. Percent of U.S. Adults With Serious Thoughts of Suicide/a Suicide Attempt and in the Past Year, 2019[455]

Demographic characteristic	Aged 18+ (2019)	Aged 18-25 (2019)	Aged 26-49 (2019)	Aged 50+ (2019)
Total	4.8 / 0.6	11.8 / 1.8	5.3 / 0.6	2.4 / 0.2
Gender				
Male	4.5 / 0.4	9.8 / 1.3	4.8 / 0.5	2.5 / 0.1
Female	5.1 / 0.7	13.7 / 2.3	5.8 / 0.6	2.3 / 0.3
Hispanic origin and race				
Not Hispanic or Latino	4.8 / 0.5	12.3 / 2.0	5.4 / 0.6	2.4 / 0.2
White	5.0 / 0.5	13.1 / 1.8	5.9 / 0.5	2.6 / 0.2
Black or African American	4.0 / 0.8	10.0 / 2.4	4.3 / 0.9	1.4 / 0.1
American Indian/Alaska Native	5.1 / 0.5	11.4 / 1.8	5.0 / 0.6	*
Native Hawaiian/Pacific Islander	2.3 / 0.4	*	0.9 / 0.1	*
Asian	3.6 / 0.4	9.1 / 2.0	3.5 / 0.2	1.6 / *
Two or more races	6.9 / 1.5	15.9 / 4.5	6.9 / 1.2	* / 0.1
Hispanic or Latino	5.0 / 0.6	10.0 / 1.2	4.9 / 0.6	2.2 / 0.2

* = low precision.

Table 5. Most Commonly Used and Recommended Depression, Anxiety, and Suicide Risk Screening Tools for Relevant Patient Populations

Condition	Instrument	No. of items (range of scores)	Typical cut-points
Depression	Patient Health Questionnaire–Depression (PHQ-9)[269, 457] (2-item version is also available)[458]	9 (0 to 27)	<5 = minimal 5 to 9 = mild 10 to 14 = moderate 15 to 19 = moderately severe 20 to 27 = severe
	Patient Health Questionnaire–Panic Disorder (PHQ-PD)[269]	5 (NA, algorithm used)	NA, positive score is indicated if questions 3a–d are all answered with yes (sum score 4) in combination with four or more other items of question 4 answered with yes (sum score ≥4)
	Center for Epidemiologic Studies Depression Scale (CES-D)[459, 460]	20 (0 to 60)	≥16
	Edinburgh Postnatal Depression Scale (EPDS)[461]	10 (0 to 30)	0 to 9 = mild distress 10 to 12 = moderate distress 13 = high likelihood of diagnosis
	Geriatric Depression Scale, 15-item (GDS Short Form)[462]	15 (0 to 15)	≥6
Anxiety	Generalized Anxiety Disorder scale (GAD), 2- and 7-item versions[29, 270]	2 (0 to 6)	≥3
		7 (0 to 21)	0 to 4 = minimal 5 to 9 = mild 10 to 14 = moderate 15 to 21 = severe
	EPDS-Anxiety subscale[463]	3 0 to 9	≥6
	Geriatric Anxiety Scale (GAS),[464] GAS-10	30 (0 to 75)	NR
		10 (0 to 30)	NR
	Geriatric Anxiety Inventory (GAI),[465] GAI-Short Form (GAI-SF)[466]	20 (0 to 20)	≥11
		5 (0-5)	≥3

Table 5. Most Commonly Used and Recommended Depression, Anxiety, and Suicide Risk Screening Tools for Relevant Patient Populations

Condition	Instrument	No. of items (range of scores)	Typical cut-points
Depression and anxiety	Patient Health Questionnaire–Anxiety-Depression Scale (PHQ-ADS)[467] (Combination of the PHQ-9 and GAD-7)	16 (0 to 48)	0 to 9 = minimal 10 to 19 = mild 20 to 29 = moderate 30 to 48 = severe
Suicide risk	PHQ-9 suicide item[269, 457]	1 (0 to 1)	1
	Columbia-Suicide Severity Rating Scale (C-SSRS)[468]	6 (NA, algorithm used)	NA, 4 levels of risk with different clinical actions
	SAD PERSONS Scale[469]	10 (0 to 10)	0 to 4 = low 5 to 6 = moderate 7 to 10 = high
	Manchester Self-Harm Rule[470]	4 (NA)	Yes to any item
	ReACT Self-Harm Rule[471]	4 (NA)	Yes to any item
	Beck Hopelessness Scale[472]	20 (0 to 20)	0 to 3 = normal 4 to 8 = mild hopelessness 9 to14 = moderate hopelessness >14 = severe hopelessness
	SAFE-T[473]	NA, semi-structured assessment	Assessment of risk level (Low, Moderate, or High) based on clinical judgement, after completing proposed steps 1 through 3

Abbreviations: EPDS-Anxiety subscale = Edinburgh Postnatal Depression Scale - Anxiety subscale; NA = not applicable; NR = not reported; SAD PERSONS = Sex, Age, Depression, Previous attempt, Ethanol abuse, Rational thinking loss, Social supports lacking, Organized plan, No spouse, Sickness; SAFE-T = Suicide Assessment Five-step Evaluation and Triage.

Table 6. Pharmacotherapy Treatment

Drug class	Generic names
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram, escitalopram, fluoxetine, fluvoxamine (CR), paroxetine (CR), sertraline
Selective serotoninin norephinephrine re-uptake inhibitors (SNRI)	Desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine (XR)
Atypical agents	Bupropion, mirtazapine
Serotonin modulators	nefazodone, trazodone, vilazodone, vortioxetine
Tricyclic and tetracyclic antidepressants	Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, ma protiline, nortriptyline, protriptyline, trimipramine
Azapirone	Buspirone
Neuroactive steroid gamma-aminobutyric acid (for perinatal depression only)	Brexanolone
Antimanic agents (for suicide risk only)	Lithium
Benzodiazepines (for anxiety only)	Alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam, quazepam

Abbreviations: CR = controlled release; XR = extended release.

Table 7. Other Relevant Guidelines on Screening for Depression, Anxiety, and Suicide

Condition	Organization, year	Recommendation(s)
Depression	American Academy of Family Physicians (AAFP), 2018	The AAFP recommends screening for depression in the general adult population. Screening must be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate followup. Pregnant women should be screened for depression at least once during the perinatal period using a validated screening instrument such as the Edinburgh Postnatal Depression Scale or the PHQ-9. Consider screening at least once during pregnancy and again 4 to 8 weeks after delivery.[115] These recommendations are based on the 2016 USPSTF recommendation.[133]
	American Academy of Pediatrics (AAP), 2019	The AAP recommends that pediatricians screen mothers for postpartum depression at the infant's 1-, 2-, and 4-month visits.[123]
	American College of Physicians (ACP), 2013	The ACP recommends clinicians screen for depression as the first step in a systematic evaluation of mood disorders in all adults. Adults who are postpartum, have a personal or family history of depression, or have comorbid medical illnesses are at increased risk. The ACP states the PHQ-2 is a widely used and efficient screening tool for depression.[474]
	American College of Preventive Medicine (ACPM), 2009	ACPM recommends universal screening for depression for all adults and that the earliest and best opportunities to identify depression are in the clinics of primary care providers.[116]
	American College of Obstetricians and Gynecologists (ACOG), 2018	ACOG recommends that all obstetrician–gynecologists and other obstetric care providers complete a full assessment of mood and emotional well-being (including screening for postpartum depression and anxiety with a validated instrument) during the comprehensive postpartum visit for each patient. If a patient is screened for depression and anxiety during pregnancy, additional screening should then occur during the comprehensive postpartum visit. There is evidence that screening alone can have clinical benefits, although initiation of treatment or referral to mental health care providers offers maximum benefit.[5] All patients with depression should be evaluated for suicidal thinking and previous suicide attempts; this evaluation is best done by direct questioning. If a woman has specific plans or significant risk of suicide, such as prior attempts or hopelessness, a mental health specialist should be consulted immediately.[475]
	American Psychiatric Association (APA), 2018	All perinatal patients should be evaluated for depressive, anxiety, and psychotic disorders throughout the pregnancy and postpartum period. We recommend screening for depression with a validated screening tool twice during pregnancy, once in early pregnancy for pre-existing psychiatric disorders and once later in the pregnancy; we also recommend postpartum patients be screened for depression during pediatric visits throughout the first 6 months postpartum as recommended by the American Academy of Pediatrics. A systematic response to screening should be in place to ensure that psychiatric disorders are appropriately assessed, treated, and followed.[476]
	Association of Women's Health,	All pregnant and postpartum women should be screened for mood and anxiety disorders. Nurses are in key positions to screen women, provide education regarding perinatal mood and anxiety disorders to pregnant and postpartum women and their families, and ensure appropriate treatment referrals.[477]

Table 7. Other Relevant Guidelines on Screening for Depression, Anxiety, and Suicide

Condition	Organization, year	Recommendation(s)
	Obstetric and Neonatal Nurses (AWHONN), 2022	
	Canadian Task Force on Preventive Health Care (CTFPHC), 2013	The CTFPHC recommends against routinely screening for depression in adults who are at average risk of depression or in subgroups of the population who may be at increased risk of depression.[120]
	Centre of Perinatal Excellence (COPE), 2017	COPE endorses using the Edinburgh Postnatal Depression Scale (EPDS) to screen for a possible depressive disorder in the perinatal period and to arrange further assessment of perinatal women with an EPDS score ≥13. The recommended timeline for screening is as follows:[124] ii. Complete the first antenatal screening as early as practical in pregnancy and repeat screening at least once later in pregnancy. iii. Complete the first postnatal screening 6–12 weeks after birth and repeat screening at least once in the first postnatal year. iv. For a woman with an EPDS score between 10 and 12, monitor and repeat the EPDS in 2–4 weeks as her score may increase subsequently. v. Repeat the EPDS at any time in pregnancy and in the first postnatal year if clinically indicated.
	Community Preventive Services Task Force (CPSTF), 2010	The CPSTF recommends collaborative care for managing depressive disorders, which includes improving the routine screening and diagnosis of depressive disorders and increasing provider use of evidence-based protocols for proactive management of diagnosed depressive disorders. The CPSTF recommends primary providers actively screen for and diagnose depressive disorders, initiate treatment for depression, and refer patients to mental health specialists as needed.[117]
	National Institute for Health and Care Excellence (NICE), 2009	NICE encourages providers to conduct a brief, question-based screener to patients who may have depression; if patients answer “yes” to either question, providers should refer the patient to a mental health provider or conduct further screening using a validated tool, such as the PHQ-9 or HADS.[121, 478]
	Institute for Clinical Systems	ICSI endorses universal screening for suspected depression based on patient presentation, risk factors, and special populations (e.g., pregnant and postpartum persons, individuals with cognitive impairment). ICSI recommends the use of a standardized screening instrument (such as the PHQ-9) and use of DSM-5 criteria.[118]

Table 7. Other Relevant Guidelines on Screening for Depression, Anxiety, and Suicide

Condition	Organization, year	Recommendation(s)
	Improvement (ICSI), 2016	
	UK National Screening Committee (NSC)	UK NSC does not recommend screening for depression in adults or in new mothers.[479]
	VA/DoD, 2022	The VA/DoD suggest that all patients not currently receiving treatment for depression be screened for depression. If screening results are positive, followup should be standard clinical practice. States that providers may use any validated instrument for appropriate populations, but the PHQ-2 is recommended within the VA and DoD. Recommends pregnant and postpartum women be screened for depression during their initial antenatal and postnatal visits; in addition, states screening to be repeated in the postpartum period at 4 to 6 weeks and 3 to 4 months after birth.PHQ-2 and PHQ-9 are the primary recommended screening and assessment tools in older populations.[119]
Anxiety	National Institute for Health and Care Excellence (NICE), 2011	NICE encourages providers to be alert to possible anxiety disorders in patients and to consider asking the person about their feelings of anxiety and their ability to stop or control worry, using the 2-item Generalized Anxiety Disorder scale. NICE includes next steps depending on GAD-2 responses.[125]
	Centre of Perinatal Excellence (COPE), 2017	COPE advises providers to include anxiety screening in the broader clinical assessment of all perinatal women due to its high prevalence. As part of the clinical assessment, use anxiety items from other screening tools (e.g., EPDS items 3, 4, and 5; DASS anxiety items and K-10 items 2, 3, 5, and 6) and relevant items in structured psychosocial assessment tools (e.g., ANRQ).[124]
	American College of Obstetricians and Gynecologists (ACOG), 2018	ACOG recommends that all obstetrician–gynecologists and other obstetric care providers complete a full assessment of mood and emotional well-being (including screening for postpartum depression and anxiety with a validated instrument) during the comprehensive postpartum visit for each patient. If a patient is screened for depression and anxiety during pregnancy, additional screening should then occur during the comprehensive postpartum visit. There is evidence that screening alone can have clinical benefits, although initiation of treatment or referral to mental health care providers offers maximum benefit.[5]
	American Psychiatric Association (APA), 2018	All perinatal patients should be evaluated for depressive, anxiety, and psychotic disorders throughout the pregnancy and postpartum period. We recommend screening for depression with a validated screening tool twice during pregnancy, once in early pregnancy for pre-existing psychiatric disorders and once later in the pregnancy; we also recommend postpartum patients be screened for depression during pediatric visits throughout the first 6 months postpartum as recommended by the American Academy of Pediatrics. A systematic response to screening should be in place to ensure that psychiatric disorders are appropriately assessed, treated, and followed.[476]

Table 7. Other Relevant Guidelines on Screening for Depression, Anxiety, and Suicide

Condition	Organization, year	Recommendation(s)
	Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN), 2022	All pregnant and postpartum women should be screened for mood and anxiety disorders. Nurses are in key positions to screen women, provide education regarding perinatal mood and anxiety disorders to pregnant and postpartum women and their families, and ensure appropriate treatment referrals.[477]
	Women's Preventive Services Initiative (WPSI), 2020	The WPSI recommends considering screening adolescents (≥13 years) and adult women (including pregnant and postpartum women) who have not been recently screened for anxiety. Clinical judgment should be used to determine screening frequency in those without a diagnosis of anxiety.[480]
Suicide risk	Department of Veterans Affairs and the Joint Commission, 2019	The VA and Joint Commission both endorse universal screening to identify individuals at-risk of suicidal behavior (the PHQ-9, item 9, is recommended). They also recommend an assessment of risk factors as part of a comprehensive evaluation of suicide risk.[127, 128]
	Canadian Coalition for Seniors' Mental Health, 2006	Healthcare providers should assess for suicide risk.[129]
	Michigan Quality Improvement Consortium, 2019	The Michigan Quality Improvement Consortium recommends to assess risk of suicide in individuals diagnosed with a depressive disorder at each encounter addressing depression until patient is treated to remission.[130] It also recommends education and counseling for suicide threats among parents, children, and adolescents, as well as annual screening for psychological, behavioral, depression, and suicide among those ages 10 to 21 years.[481]

Abbreviations: ANRQ = ANtenatal Risk Questionnaire; DASS = Depression Anxiety Stress Scales; DoD = Department of Defence; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; EPDS = Edinburgh Postnatal Depression Scale; GAD-2 = generalized anxiety disorder 2-item scale; HADS = Hospital Anxiety and Depression Scale; PHQ = Patient Health Questionnaire; VA = Veterans Affairs.

Table 8. Characteristics of Depression Screening Studies (KQ1)

Author, Year	Quality rating	Study design (unscreened control?)	All have sx?	Study N	Broad population	Country	Specific population	FUP, wks	Screening approach	Condition criteria	Benefit (KQ1)	Harm (KQ3)
Bergus, 2005[149]	Fair	RCT (No)	Yes	59	General adults	USA	Adult primary care patients in rural clinics screening positive for depression.	4, 10, 24	Screening results	PHQ-2 positive	X	
Bijl, 2003[154]	Fair	Cluster RCT (No)	Yes	145	Older adults	NLD	Primary care patients age ≥55 years with MDD.	8, 26, 52	Screening results, GP training	GDS ≥5 and PRIME-MD interview positive	X	
Callahan, 1994[155]	Fair	Cluster RCT (No)	Yes	175	Older adults	USA	Medically indigent primary care patients age ≥60 years screening positive for depression.	4, 13, 26, 39	Screening results, treatment protocol	CES-D ≥16 and HAM-D ≥15	X	
Glavin, 2010[158]	Fair	CCT (No)	No	2,247	Postpartum	NOR	Postpartum patients age ≥ 18 years in participating municipality.	p13, p26	Screening results, redesigned postpartum care	NA (all included)	X	
Jarjoura, 2004[150]	Fair	RCT (No)	Yes	61	General adults	USA	Primary care patients age ≥18 years screening positive for depression and not	26, 52	Screening results, treatment protocol	Positive response on the PRIME-MD	X	

Table 8. Characteristics of Depression Screening Studies (KQ1)

Author, Year	Quality rating	Study design (unscreened control?)	All have sx?	Study N	Broad population	Country	Specific population	FUP, wks	Screening approach	Condition criteria	Benefit (KQ1)	Harm (KQ3)
							currently receiving or seeking mental health treatment.					
Kroenke, 2018[165]	Good	RCT (No)	Yes	300	General adults	USA	Primary care patients age ≥18 years screening positive for sleep, pain, anxiety, depression, or fatigue symptoms.	13	Screening results	Scored ≥4 (out of 10) on anxiety, depression, sleep, fatigue, or pain sx	X	
Leung, 2011[159]	Good	RCT (Yes)	No	462	Postpartum	HKG	Patients at 8 weeks postpartum at participating maternal health centers.	p26, p78	Screening	NA (all included)	X	X
MacArthur, 2002[160]	Fair	Cluster RCT (Yes)	No	2,064	Postpartum	GBR	General practice patients at 4 weeks postpartum.	p17	Screening, midwife training in depression care	NA (all included)	X	
Morrell, 2009[161]	Fair	Cluster RCT (No)	No	3,449	Postpartum	GBR	Adults age ≥18 years at 6 weeks postpartum at	p26	Screening results, health visitor-delivered counseling	NA (all included)	X	

Table 8. Characteristics of Depression Screening Studies (KQ1)

Author, Year	Quality rating	Study design (unscreened control?)	All have sx?	Study N	Broad population	Country	Specific population	FUP, wks	Screening approach	Condition criteria	Benefit (KQ1)	Harm (KQ3)
							participating practices.					
Rost, 2001[151]	Good	Cluster RCT (No)	Yes	479	General adults	USA	Primary care patients age ≥18 years screening positive for depression.	26, 52, 104	Screening results, provider training and supports	WHO-CIDI-positive and IDD ≥5	X	
van der Weele, 2012[156]	Good	Cluster RCT (No)	Yes	239	Older adults	NLD	Adults age ≥75 years registered at participating practices screening positive for untreated depression.	26, 52	Screening results, referral for stepped care	GDS-15 ≥5	X	
van der Zee, 2017[162]	Fair	CCT (Yes)	No	3,089	Postpartum	NLD	Patients at 2–3 weeks postpartum visiting participating well-child care centers.	p39, p52	Screening, PCP training and supports	NA (all included)	X	
Wells, 2000[152]	Fair	Cluster RCT (No)	Yes	1,356	General adults	USA	Primary care patients age ≥18 years screening positive for depression.	26, 52, 104, 290	IG1: Screening results, PCP training and supports, tx	Positive on WHO CIDI-2	X	

Table 8. Characteristics of Depression Screening Studies (KQ1)

Author, Year	Quality rating	Study design (unscreened control?)	All have sx?	Study N	Broad population	Country	Specific population	FUP, wks	Screening approach	Condition criteria	Benefit (KQ1)	Harm (KQ3)
	Fair	Cluster RCT (No)	Yes	1,356	General adults	USA	Primary care patients age ≥18 years screening positive for depression.	26, 52, 104, 290	IG2: Screening results, PCP training and supports, CBT	Positive on WHO CIDI-2	X	
	Fair	Cluster RCT (No)	Yes	1356	General adults	USA	Primary care patients age ≥18 years screening positive for depression.	26, 52, 104, 290	IG3: Screening results, PCP training and supports, medication adherence	Positive on WHO CIDI-2	X	
Whooley, 2000[157]	Fair	Cluster RCT (No)	Yes	331	Older adults	USA	Primary care patients age ≥65 years screening positive for depression.	104	Screening results, brief provider training	GDS ≥6	X	
Wickberg, 2005[163]	Fair	Cluster CCT (No)	No	669	Pregnant	SWE	Pregnant patients registered at participating prenatal care centers.	g36	Screening results, brief midwife training	NA (all included)	X	

Table 8. Characteristics of Depression Screening Studies (KQ1)

Author, Year	Quality rating	Study design (unscreened control?)	All have sx?	Study N	Broad population	Country	Specific population	FUP, wks	Screening approach	Condition criteria	Benefit (KQ1)	Harm (KQ3)
Williams, 1999[153]	Fair	RCT (Yes)	No	969	General adults	USA	Adult primary care patients.	13	IG1: Case-finding (1- or 20-item)	NA (all included)	X	
	Fair	RCT (Yes)	No	969	General adults	USA	Adult primary care patients.	13	IG2: Case-finding (20-item)	NA (all included)	X	
	Fair	RCT (Yes)	No	969	General adults	USA	Adult primary care patients.	13	IG3: Case-finding (1-item)	NA (all included)	X	
Yawn, 2012[164]	Fair	Cluster RCT (No)	No	2,343	Postpartum	USA	Patients aged ≥18 years, 5-12 weeks postpartum, receiving care at the participating family practice.	p52	Screening results, provider training and supports	NA (all included)	X	

Abbreviations: CBT = cognitive behavioral therapy; CCT = controlled clinical trial; CES-D = Center for Epidemiologic Studies Depression scale; FUP = followup; GBR = Great Britain; GDS = Geriatric Depression Scale; GP = general practice ; HAM-D = Hamilton Rating Scale for Depression; HKG = Hong Kong; IDD = Inventory to Diagnose Depression ; IG1 = intervention group 1; IG2 = intervention group 2; IG3 = intervention group 3; MDD = major depressive disorder; NA = not applicable; NLD = Netherlands; NOR = Norway; PCP = primary care provider; PHQ = Patient Health Questionnaire; PRIME-MD = Primary Care Evaluation of Mental Disorders; RCTs = randomized controlled trials; SWE = Sweden; sx = symptoms; tx = treatment; USA = United States of America; WHO CIDI = World Health Organization Composite International Diagnostic Interview; WHO CIDI-2 = World Health Organization World Mental Health Composite International Diagnostic Interview.

Table 9. Summary of Meta-Analysis Results for Depression Outcomes Among Depression Screening Studies (KQ1)

Outcome	No. studies (n analyzed)	Type of effect	Pooled result (95% CI)*	I^2, %	Tau^2	Range of effects†	Median (IQR) effects†
Prevalence (met criteria for depression or score above cutoff)							
All studies	8 (10,244)	OR	0.60 (0.50 to 0.73)	0	0.0	0.30 to 1.11 ARD: -9.1 to +1.4	0.67 (0.47 to 0.80) ARD: -5.2 (-6.8 to -2)
General	1 (218)	OR	0.67 (0.37 to 1.21)	NA	NA	0.67 ARD: -9	NA (1 effect total)
Older	1 (206)	OR	0.70 (0.38 to 1.26)	NA	NA	0.70 to 0.80 ARD: -8 to -5	NA (2 effects total)
Postpartum	5 (9,202)	OR	0.54 (0.40 to 0.73)	25.6	0.02	0.30 to 1.11 ARD: -9.1 to +1.4	0.50 (0.40 to 0.67) ARD: -5.2 (-6.1 to -1.9)
Pregnant	1 (618)	OR	0.80 (0.48 to 1.35)	NA	NA	0.80 ARD: -2	NA (1 effect total)
Remission (did not meet criteria for depression or score below cutoff, among those with symptoms at baseline)							
All studies	8 (2,302)	OR	1.58 (1.23 to 2.02)	0	0	0.81 to 4.81 ARD: -18 to +33.8	1.41 (1.14 to 1.95) ARD: 7.2 (2.9 to 15.2)
General	3 (1,396)	OR	1.52 (1.41 to 1.63)	0	0	0.81 to 4.06 ARD: -5 to +33	1.41 (1.14 to 1.70) ARD: 7.7 (3 to 14)
Older	2 (259)	OR	0.97 (0.21 to 4.41)	0	0	0.83 to 2.49 ARD: -18 to +5	1.14 (0.89 to 1.33) ARD: -0.6 (-4.7 to +3)
Postpartum	2 (562)	OR	1.83 (0.27 to 12.27)	0	0	1.67 to 2.34 ARD: 11.7 to 19	2.34 (1.67 to 2.34) ARD: 17.7 (11.7 to 19)
Pregnant	1 (85)	OR	4.81 (1.81 to 12.80)	NA	NA	4.81 ARD: 33.8	NA (1 effect total)
Combined reduced depression‡							
All studies	16 (8,448)	OR	1.63 (1.37 to 1.95)	0.5	0	--§	--§
General	5 (1,675)	OR	1.53 (1.38 to 1.70)	0	0	--§	--§
Older	4 (675)	OR	1.00 (0.56 to 1.78)	15.2	0.02	--§	--§
Postpartum	6 (6,013)	OR	1.98 (1.60 to 2.43)	0	0	--§	--§
Pregnant	1 (85)	OR	4.81 (1.81 to 12.80)	NA	NA	--§	--§
Symptom severity (change in depression symptom scores)							
All studies	9 (5,543)	Mean difference in change	-1.0 (-2.3 to 0.3)	74.4	1.1	-8.2 to +2.6	-1 (-2.5 to +0.3)
All studies	6 (3,790)	SMD	-.09 (-0.36 to 0.18)	79.6	0.04	NR	NR

*Effect based on restricted maximum likelihood model with the Knapp-Hartung adjustment for small samples.
†Range of effects for all study arms, subgroup analyses, and timepoints (i.e., not limited to records in the meta-analysis).
‡As available, selected depression remission or scoring below a cutoff first, depression prevalence or scoring above a cutoff (reversed) second, and depression response third.

Table 9. Summary of Meta-Analysis Results for Depression Outcomes Among Depression Screening Studies (KQ1)

[§]Not shown because reversal of results from some studies creates misleading ARD values.

Abbreviations: ARD = absolute risk difference; CI = confidence interval; IQR =interquartile range; NA = not applicable; NR = not reported; OR = odds ratio; SMD = standardized mean difference.

Table 10. Summary of Participant Demographic Characteristics Among Studies of Depression Screening (KQ1): Weighted Mean (Number of Studies Reporting), Unless Otherwise Indicated

Population	No. of studies (No. US-based studies)	Total N	Mean age	% Women*	Race or ethnicity (US-based studies only [k=9])	Race or ethnicity, range of % of participants among US-based studies
All	17 (9)	18,437	38.2 (13)	93.6 (17)	Black: 17.6 (6) Asian/Asian-Amer: 7.5 (1) Native Amer/AN: NR (0) Hispanic/Latino: 25.4 (4) White: 51.3 (6)	Black: 7.1 to 51.2 Asian/Asian-Amer: NA Native Amer/AN: NA Hispanic/Latino: 4.5 to 59.3 White: 29 to 94.1
General	6 (6)	3,224	48.3 (6)	72.7 (6)	Black: 13.1 (3) Asian/Asian-Amer: NR (0) Native Amer/AN: NR (0) Hispanic/Latino: 25.4 (2) White: 51.3 (5)	Black: 7.1 to 49.3 Asian-Amer/PI: NA Native Amer/AN: NA Hispanic/Latino: 29.6 to 59.3 White: 29 to 94.1
Older	4 (2)	890	73.3 (4)	66.3 (4)	Black: 39.0 (2) Asian/Asian-Amer: 7.5 (1) Native Amer/AN: NR (0) Hispanic/Latino: 4.5 (1) White: 43.9 (1)	Black: 32.6 to 51.2 Asian-Amer/PI: NA Native Amer/AN: NA Hispanic/Latino: NA White: NA
Postpartum	6 (1)	13,654	29.9 (3)	100* (0)	Black: 18.0 (1) Asian/Asian-Amer: NR (0) Native Amer/AN: NR (0) Hispanic/Latino: 12.0 (1) White: NR (0)	NA
Pregnant	1 (0)	669	NR	100* (0)	NR	NA

*Gender was not reported in studies of perinatal patients so participants are counted as women, recognizing that there may be some individuals who do not identify as women; non-binary/gender nonconforming categories were not reported in any studies.

Abbreviations: Amer = American; Native Amer/AN = Native American/Alaska Native; NA = not applicable; NR = not reported; US = United States.

Table 11. Summary of Intervention Components in Addition to Screening in Depression Screening Studies (KQ1)

Author, Year	Tng in Screening	Tng in Diagnosis	Tng in treatment	Generic tx guide	Generic handout	Pt-specific tx rec	Referral support	Sx monitoring	Monitoring med use	Med use counseling	Therapeutic approach	IG Num Sessions	PCP Role
General adults													
Bergus, 2005[149]											NA	NA	Most/ all
Jarjoura, 2004[150]			X	X	X		X				NA	NA	Most/ all
Kroenke, 2018[165]											NR	NA	Most/ all
Rost, 2001[151]	X	X	X	X	X		X	X	X	X	NA	NA	Some
Wells, 2000[152]		X	X	X	X		X	X	X	X	CBT, Medication management	NR	Some
Wells, 2000[152]		X	X	X	X		X	X	X	X	CBT	NR	Some
Wells, 2000[152]		X	X	X	X		X	X	X	X	Medication management	NR	Some
Williams, 1999[153]											NA	NA	Most/ all
Williams, 1999[153]											NA	NA	Most/ all
Williams, 1999[153]											NA	NA	Most/ all
Older adults													
Bijl, 2003[154]	X	X	X								NA	NA	Most/ all
Callahan, 1994[155]				X	X	X					PCP followup visits	3	Most/ all
van der Weele, 2012[156]										X	CBT	1-2 (home visits), 10 (group)	Some
Whooley, 2000[157]		X	X	X							Psycho-education group	6 (group), 1 (booster group)	Some

Table 11. Summary of Intervention Components in Addition to Screening in Depression Screening Studies (KQ1)

Author, Year	Tng in Screening	Tng in Diagnosis	Tng in treatment	Generic tx guide	Generic handout	Pt-specific tx rec	Referral support	Sx monitoring	Monitoring med use	Med use counseling	Therapeutic approach	IG Num Sessions	PCP Role
Perinatal													
Glavin, 2010[158]		X	X	X	X						Non-directive	≥1	None
Leung, 2011[159]											Non-directive	NR	Most/ all
MacArthur, 2002[160]			X	X							NA	NA	None
Morrell, 2009[161]		X	X	X							CBT	≤8	None
van der Zee, 2017[162]	X			X			X				NA	NA	Some
Wickberg, 2005[163]		X	X								NA	NA	None
Yawn, 2012[164]	X	X	X	X	X		X	X	X	X	NR	1-6 (median: 1)	Some

Abbreviations: CBT = cognitive behavioral therapy; IG = intervention group; NA = not applicable; NR = not reported; Num = number; PCP = primary care provider; pt = patient; sx = symptoms; Tng = training; tx = treatment.

Table 12. Characteristics of Primary Studies Examining Test Accuracy of the Geriatric Depression Scale for Detecting Depression (KQ2)

Author, year	Quality	Country	Brief population description	N Screened and analyzed	Diagnostic interview	Diagnostic criteria	Screening test	Condition
Alves Apostolo, 2018[166]	Fair	Portugal	Older than 65 years*	139	Unspecified semi-structured interview	DSM-5	GDS-15	MDD
Blank, 2004[167]	Fair	USA	60 years and older*	360	DIS	DSM-IV	GDS-15	MDD
							GDS-30	MDD
Broekman, 2011[168]	Fair	Singapore	Regular social services users 60 years and older*	4253	SCID	DSM-IV	GDS-15	MDD
							GDS-7	MDD
Davison, 2009[169]	Good	Australia	Assisted living residents*	168	SCID	DSM-IV	GDS-15	MDD
Eriksen, 2019[170]	Fair	Norway	Community-dwelling adults 60 years and older	194	Unspecified structured interview	ICD-10	GDS-5	Any symptom of depression
Izal, 2010[171]	Fair	Spain	60 years or older	105	SCID	DSM-IV	GDS-5	MDD
							GDS-10	MDD
							GDS-15	MDD
							GDS-30	MDD
							GDS-R	MDD
Jung, 2019[172]	Fair	The Republic of Korea	Outpatients 60 years and older*	385	MINI	DSM-IV	GDS-15	Minor and major depressive disorder
								MDD
Licht-Strunk, 2005[173]	Fair	The Netherlands	Visiting the GP age 55 and older*	948	PRIME-MD	DSM-IV	GDS-15	MDD
Marc, 2008[174]	Fair	USA	New admission age 65 years and older	492	SCID	DSM-IV	GDS-15	MDD
Pellas, 2021[175]	Fair	Sweden	65 years and older	113	MINI	DSM-5	GDS-15	MDE

Table 12. Characteristics of Primary Studies Examining Test Accuracy of the Geriatric Depression Scale for Detecting Depression (KQ2)

Author, year	Quality	Country	Brief population description	N Screened and analyzed	Diagnostic interview	Diagnostic criteria	Screening test	Condition
Rait, 1999[176]	Fair	UK	Community African Caribbean resident age 60 years or older	130	GMS-AGECAT	Geriatric Mental Scale	GDS-15	Score ≥3 (depression)
Shin, 2019[177]	Fair	The Republic of Korea	60 years and older*	774	Unspecified structured interview	DSM-IV	GDS-15	MDD
Stefan, 2017[178]	Fair	Romania	60 years and older*	172	Unspecified semi-structured interview	DSM-IV	GDS-15	MDD
							GDS-30	MDD
van Marwijk, 1995[179]	Fair	The Netherlands	65 years and older*	586	DIS	DSM-IV	GDS-1	MDD
							GDS-4	MDD
							GDS-10	MDD
							GDS-15	MDD
							GDS-30	MDD

*****Excluded participants with low cognitive function scores or with a diagnosis of major neurocognitive disorder or dementia.

Abbreviations: DIS = diagnostic interview schedule; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; GDS = Geriatric Depression Scale; GMS AGECAT = Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy; GP = general practice; ICD = International Statistical Classification of Diseases; MDD = major depressive disorder; MDE = major depressive episodes; MINI = Mini-International Neuropsychiatric Interview; N = number of participants; PRIME-MD = Primary Care Evaluation of Mental Disorders; SCID = Structured Clinical Interview for DSM Disorders; UK = United Kingdom; USA = United States of America.

Table 13. Characteristics of ESRs of Test Accuracy of Screening Tools to Detect Major Depression

Screening Test	Author, year	No. of studies	Reference standards	No. of participants	No. with depression (%)
PHQ-9 Linear	Negeri, 2021[188]*	100	Fully structured diagnostic interview Semi-structured diagnostic interview (excluding MINI), MINI	44,503	4,541 (10.2)
	Wang, 2021[185]	4	Fully structured diagnostic interview Semi-structured diagnostic interview	2,344	85 (5.8)†
PHQ-9 Algorithm	He, 2020[181]*	54	Fully structured diagnostic interview Semi-structured diagnostic interview (excluding MINI), MINI	16,688	2,091 (13)
PHQ-8	Wu, 2020[186]*	54	Fully structured diagnostic interview Semi-structured diagnostic interview (excluding MINI), MINI	16,742	2,097 (12.5)
PHQ-4	Harel, 2022[187]*	75	Fully structured diagnostic interview Semi-structured diagnostic interview (excluding MINI), MINI	34,698	3,392 (9.8)
PHQ-2, PHQ-2+PHQ-9	Levis, 2020[183]*	100	Fully structured diagnostic interview Semi-structured diagnostic interview (excluding MINI), MINI	44,318	4,572 (10.3)
Whooley	Bosanquet, 2015[180]	10	Diagnostic interview	4,618	602 (13.0)
	Smith, 2022[189]	5	Diagnostic interview	1,402	115 (9.6)
CES-D	Vilagut, 2016[184]	28	Standardized diagnostic interview	10,617	807 (7.6)
EPDS	Levis, 2020[183]*	58	Fully structured diagnostic interview Semi-structured diagnostic interview (excluding MINI), MINI	15,557	2,069 (13.3)

* IPD meta-analysis.
† k=3, n=1,465.

Abbreviations: CES-D = Center for Epidemiologic Studies Depression scale; EPDS = Edinburgh Postnatal Depression Scale; MINI = Mini International Neuropsychiatric Interview; PHQ = Patient Health Questionnaire.

Table 14. Participant Characteristics for Studies of Test Accuracy of Depression Screening Instruments (KQ2)

Author, year	N analyzed	Major depressive disorder, n (%)	Mean age, years	Age range, years	% Women*	Race or ethnicity, %	SES
Alves Apostolo, 2018[166]	139	23 (16.5)	78	65-96	60	NR	Mean education, years: 5.6
Blank, 2004[167]	125	14 (11.2)	76.8	≥60	76	White: 90 Other: 10	Education, % 6th grade or less: 0 7-11th grade: 35 12th grade or more: 65 Annual income, % <10,000: 19 10-19,999: 52 20-29,999: 9 30-39,999: 11 ≥40,000: 9
Broekman, 2011[168]	4,253	147 (3.5)	74	≥60	59	Asian: 100	NR
Davison, 2009[169]	168	27 (16.1)	85	67-97	77	NR	NR
Eriksen, 2019[170]	194	56 (28.9)†	73.4	≥60	74	NR	NR
Izal, 2010[171]	105	9 (8.6)	73	≥60	58	NR	NR
Jung, 2019[172]	385	45 (11.7)	70.2	60-85	60.0	NR	Education, % <6 years: 45.0 6-12 years: 45.2 >12 years: 9.8 Self-reported SES, % High: 5.8 Middle: 71.1 Low: 22.1
Licht-Strunk, 2005[173]	948	NA (13.7)‡	NR	≥55	64.5	NR	NR
Marc, 2008[174]	492	71 (14.4)	78.3	≥65	65.1	White: 85.0 Black: 10.4 Hispanic: 3.9	Educational attainment, % <High school: 30.6 High school: 31.7 Some college: 17.0 College: 9.9 Post-college: 10.8
Pellas, 2021[175]	113	17 (15.0) §	76	≥65	74	NR	NR

Table 14. Participant Characteristics for Studies of Test Accuracy of Depression Screening Instruments (KQ2)

Author, year	N analyzed	Major depressive disorder, n (%)	Mean age, years	Age range, years	% Women*	Race or ethnicity, %	SES
Rait, 1999[176]	130	13 (10)**	69 (Jamaican only)	≥60	50 (Jamaican only)	Black: 100	NR
Shin, 2019[177]	774	30 (3.9)	69	≥60	60	NR	Mean total educational years: 7.19
Stefan, 2017[178]	172	24 (14.0)	74	60-89	60	NR	Average years of education: 10
van Marwijk, 1995[179]	586	33 (5.6)	74	65-94	60	NR	NR

*****Non-binary/gender nonconforming categories were not reported in any studies.
†Any symptom of depression, identified using ICD-10.
‡Adjusted for partial verification.
§Major depressive episodes.
**Depression identified using the Geriatric Mental Scale with a depression score of 3 or more.

Abbreviations: ICD-10 = International Statistical Classification of Diseases, 10th revision; N = number of participants; NA = not applicable; NR = not reported; SES = socioeconomic status.

Table 15. Characteristics of Existing Systematic Reviews Included to Address the Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Cuijpers database	Quality	Outcomes	Population	Intervention	Last search date	Total # of included studies	Total N	Included study designs (Note if conducted IPD analysis)
Aherne, 2017[191]	No	Good	Depression	Moderate-level depression	Psychological	Jan-2014	4 CBT (14 total)	1,743	RCTs, ESRs
Castro, 2020[192]	No	Good	Depression	General population	Telemedicine	Sep-2017	10	1,392	RCTs
Collado, 2016[193]	No	Good	Depression	Hispanic/Latino	Psychological	Jul-2015	36 (22 RCT and 14 OLT)	NR	RCTs, open-label trial
Cuijpers, 2017[194]	Yes	Good	Depression, Anxiety, QoL or functioning, Maternal or fetal, Suicide-related	General population	Psychological	NR	NR	NR	RCTs, ESRs
Cuijpers, 2018[197]	Yes	Good	Depression	General population	Psychological	Jan-2016	256	34,921	RCTs
Cuijpers, 2019[196]	Yes	Good	Depression	General population	Psychological	Jan-2019	289 (369 comparisons)	NR	RCTs
Cuijpers, 2019[198]	Yes	Good	Depression	General population	Psychological	Jan-2019	140	15,419	RCTs
Cuijpers, 2020[195]	Yes	Good	Depression	General population	Psychological	Jan-2018	309 (385 comparisons)	NR	RCTs
Driessen, 2015[199]	Yes	Good	Depression	General population	Psychological	Jun-2013	57	2,103	RCTs
Harerimana, 2019[200]	No	Good	Depression	Older adults	E-interventions	Nov-2017	9	2,032	RCTs, Obsrv, QuasiRCT
Harper Shehadeh, 2016[201]	No	Good	Depression, Anxiety	Specific racial/ethnic	Self-help (or minimally guided)	Jul-2015	8	NR	RCTs, nonrandomized experimental studies
Holvast, 2017[202]	No	Good	Depression	Older adult primary care patients	Psychological	Jan-2017	11 (10 RCTs and 1 cohort study)	1,543 (1,529 RCT, 14 cohort)	No restrictions

Table 15. Characteristics of Existing Systematic Reviews Included to Address the Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Cuijpers database	Quality	Outcomes	Population	Intervention	Last search date	Total # of included studies	Total N	Included study designs (Note if conducted IPD analysis)
Huang, 2018[203]	No	Good	Depression	Perinatal	CBT-specific	Mar-2017	20	3,623	RCTs
Karyotaki, 2017[205]	Yes	Good	Depression	General population	E-interventions	Jan-2016	13	3,876	RCTs (IPD)
Karyotaki, 2018[204]	Yes	Good	Depression	General population	E-interventions	Jan-2016	24	4,889	RCTs (IPD)
Letourneau, 2017[206]	No	Good	Depression	Perinatal	Psychological	NR	36	>5,000	RCTs, QuasiRCT
Li, 2022[220]	No	Good	Depression, Anxiety	Perinatal	CBT-specific	Apr-2020	77 (68 in MA)	11,221	RCTs, QuasiRCT
Massoudi, 2019[207]	No	Good	Depression, Anxiety	Primary care patients	E-interventions	Jan-2018	14	4,183	RCTs
Nair, 2018[208]	No	Good	Depression	Perinatal	Telemedicine	Apr-18	10	1,138	RCTs
Nieuwenhuijsen, 2020[209]	No	Good	QoL or functioning	General population	Psychological	April-2020	45	13,669	RCTs
Pineros-Leano, 2017[210]	No	Good	Depression	Hispanic/Latino immigrant	CBT-specific	Jul-2016	11	NR	RCTs, Obsrv, QuasiRCT
Ponting, 2020[211]	No	Good	Depression	Perinatal Black and Hispanic/Latino	Psychological	Sep-2018	13 (10 RCTs)	1,971	RCTs, CCTs
Rojas-Garcia, 2015[212]	No	Good	Depression	Low SES	Any behavioral delivered in healthcare setting	Apr-2013	11 (13 comparisons)	2,261	RCTs, QuasiRCT
Roman, 2020[213]	No	Good	Depression	Perinatal	CBT-specific	2017	6	635	RCTs
Thomas, 2018[214]	No	Good	Depression	Older adults	CBT-specific	Jan-2015	53	3,568	RCTs, Nonrandomized experimental studies
Weaver, 2017[215]	No	Good	Depression, Anxiety	Rural settings	CBT-specific	Apr-2015	16	1,193	No restrictions
Weitz, 2018[216]	Yes	Good	Anxiety	General population	Psychological	Jan-2016	51	5,737	RCTs

Table 15. Characteristics of Existing Systematic Reviews Included to Address the Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Cuijpers database	Quality	Outcomes	Population	Intervention	Last search date	Total # of included studies	Total N	Included study designs (Note if conducted IPD analysis)
Xiang, 2020[217]	No	Good	Depression	Older adults	E-interventions	Nov-2017	9	1,272	RCTs, Obsrv, CCTs
Zhang, 2019[219]	No	Good	Depression	Primary care patients	Psychological	Apr-2017	65	10,951	RCTs
Zhang, 2019a[218]	No	Good	Depression	Primary care patients	CBT-specific	Nov-2018	57	10,701	RCTs

Abbreviations: CBT = cognitive behavioral therapy; CBT-specific = cognitive behavioral therapy-specific; CCTs = controlled clinical trials; E-Interventions = electronic interventions; ESRs = existing systematic reviews; IPD = individual participant data; MA = meta-analysis; N = number of participants; NR = not reported; Obsrv = observation; OLT = open label trial; QoL = quality of life; QuasiRCT = quasi-randomized controlled trial; RCTs = randomized controlled trials; RCTs (IPD) = randomized controlled trial individual participant data; SES = socioeconomic status.

Table 17. Meta-Analysis Results for Depression Remission and Depression Response in ESRs of Psychological Treatment of Depression (KQ4)

Author, Year	Quality	Outcomes	Population	Intervention	Last search date	Total # of included studies	Total N	Included study designs (Note if conducted IPD analysis)
Arroll, 2016[221]	Good	Depression	Primary care patients	AD	Oct-2015	17	NR	RCTs
Baune, 2018[222]	Good	QoL or functioning	General population	AD	Nov-2014	12	NR	RCTs, Obsrv, CCTs
Cipriani, 2018[224]	Good	Depression, Harms	General population	AD	Jan-2016	522 (814 tx groups)	116, 477	RCTs
Cuijpers, 2015[226]	Good	Depression	General population	AD, SSRIs, SNRIs, Any pharm	January-2014	53	4,740	RCTs
Krause, 2019[227]	Good	Depression, QoL or functioning, Harms	Older adults	Any pharm	Dec-2017	53	9,274	RCTs
Lee, 2018[228]	Fair	QoL or functioning	General population	AD	Jun-2017	17	NR	RCTs
Lisinski, 2020[229]	Fair	Depression, Harms	General population	Duloxetine	NR	15	3575	RCTs (IPD)
Rabinowitz, 2016[231]	Fair	Depression	General population	AD	NA	34	10,737	RCTs (IPD)
Rojas-Garcia, 2015[212]	Good	Depression	Low SES	Any pharm	Apr-2013	11 (13 comparisons)	2,261	RCTs, QuasiRCT
Viswanathan, 2021[232]	Good	Depression, QoL or functioning, Maternal or fetal, Harms	Perinatal	Any pharm	Jun-2020	164	NR	RCTs, Obsrv, CCTs

Abbreviations: AD = antidepressant; CCTs = controlled clinical trials; IPD = individual participant data; N = number of participants; NA = not applicable; NR = not reported; Obsrv = observation; pharm = pharmacotherapy; QoL = quality of life; QuasiRCT = quasi-randomized controlled trial; RCTs = randomized controlled trials; RCTs (IPD) = randomized controlled trial individual participant data; SES = socioeconomic status; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin and norepinephrine reuptake inhibitor; tx = treatment.

Table 17. Meta-Analysis Results for Depression Remission and Depression Response in ESRs of Psychological Treatment of Depression (KQ4)

Author, Year	Intervention	Outcome	Population	Control	FUP, wks	k	N analyzed	Effect	ES (95% CI)	I^2 (%)
Huang, 2018 [203]	CBT	Depression remission	Postpartum mothers	Any	Short-term	4	590	OR	6.57 (1.84 to 23.48)	60
Huang, 2018[203]	CBT	Depression remission	Postpartum mothers	Any	Long-term	9	1,558	OR	2.00 (1.61 to 2.48)	0
Karyotaki, 2018[236]	Guided internet-based	Depression remission	All participants	Any	5-13	26	4,867	OR	2.41 (2.07 to 2.79)	NR
Karyotaki, 2017[205]	Self-guided iCBT	Depression response	All participants	Any	NR	13	3,795	Standardized regression coefficient (IPD MA)	0.53 (NR, p<.05)	NA
Cuijpers, 2017[194]	Psychological (any)	Depression response	All participants	Any	52	11	NR	OR	1.59 (1.14 to 2.21)	55
Karyotaki, 2018[236]	Guided internet-based	Depression response	All participants	Any	5-13	26	4,867	OR	2.49 (2.17 to 2.85)	NR

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; ES = evidence synthesis; ESRs = existing systematic reviews; FUP = followup; iCBT = internet-based cognitive behavior therapy; IPD MA = individual participant data meta-analysis; NA = not applicable; NR = not reported; OR = odds ratio.

Table 18. Characteristics of ESRs Addressing Harms of Psychological Treatment of Depression (KQ5)

Author, Year	Cuijpers database	Quality	Outcomes	Population	Intervention	Last search date	Total # of included studies	Total N	Included study designs (Note if conducted IPD analysis)
Cuijpers, 2018[197]	Yes	Good	Harms	General population	Psychological	Jan-2017	18 (23 comparison)	1,655	RCTs
Ebert, 2016[234]	Yes	Good	Harms	General population	E-interventions (guided)	Jan-2014	18	2,079	RCTs (IPD)
Jonsson, 2016[235]	No	Good	Harms	Older adults	Psychological	May-2016	14	927	RCTs
Karyotaki, 2018[236]	Yes	Good	Harms	General population	E-interventions (self-help)	Jan-2016	13	3,805	RCTs (IPD)

Abbreviations: E-Interventions = electronic interventions; ESRs = existing systematic reviews; IPD = individual participant data; N = number of participants; RCTs = randomized controlled trials; RCTs (IPD) = randomized controlled trial individual participant data.

Table 19. Characteristics of ESRs in General Adult Populations Addressing Harms of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Quality	Outcomes	Population	Intervention	Last search date	Total # of included studies	Total N	Included study designs (Note if conducted IPD analysis)
Braun, 2016[238]	Fair	Suicide-related	General population	AD	Sep-2014; Mar-2015	29	6,934	RCTs
Chan, 2019[239]	Good	Harms	General population	AD	Nov-2018	18	2,119,627	Obsrv
Cipriani, 2018[224]	Good	Depression, Harms	General population	AD	Jan-2016	522 (814 tx groups)	116,477	RCTs
Gibbons, 2012[240]	Fair	Suicide-related	General population, Older adults	Fluoxetine, venlafaxine	NR	41	9,185 (2 deaths, 20 attempts)	RCTs (IPD)
Hengartner, 2021[241]	Good	Suicide-related	General population	SSRIs, SNA	Jan-2020	27	1,447,480	Obsrv
Jacobsen, 2019[242]	Good	Harms	General population	AD	Mar-2016	17	9,475	RCTs
Jakobsen, 2017[243]	Good	Harms, Suicide-related	General population	SSRIs	Jan-2016	195 (131 in MA)	27,422	RCTs
Jensen, 2019[244]	Good	Harms	General population	SSRIs	Dec-2017	30 (3 RCTs, 27 obs)	>845,655	RCTs, Obsrv
Kaminski, 2020 [245]	Fair	Suicide-related	General population	2nd gen AD	2016	14 investigational AD programs	40,857	RCTs
Khanassov, 2018[246]	Good	Harms	General population	SSRIs and SNRIs	Nov-2016	33	>1.3 million	Obsrv
Kunutsor, 2018[248]	Good	Harms	General population	AD	Apr-2018	8	960,113 (9,027 VTEs)	Obsrv
Maslej, 2017[249]	Good	Harms	General population	AD	Jun-2014	16 (1 RCTs, 15 obs)	378,400	RCTs, Obsrv
Na, 2018[250]	Good	Harms	General population	Bupropion, Mirtazapine	May-2017	7	128,480	Obsrv
Naslund, 2018[251]	Fair	Suicide-related	General population	SSRIs	NR	28	8,262	RCTs (IPD)

Table 19. Characteristics of ESRs in General Adult Populations Addressing Harms of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Quality	Outcomes	Population	Intervention	Last search date	Total # of included studies	Total N	Included study designs (Note if conducted IPD analysis)
Trajkova, 2019[253]	Good	Harms	General population	AD	Sep-2018	31	3,103,686	Obsrv

Abbreviations: AD = antidepressant; CCTs = controlled clinical trials; ESRs = existing systematic reviews; IPD = individual participant data; MA = meta-analysis; N = number of participants; NR = not reported; Obsrv or obs = observation; pharm = pharmacotherapy; QoL = quality of life; QuasiRCT = quasi-randomized controlled trial; RCTs = randomized controlled trials; RCTs (IPD) = randomized controlled trial individual participant data; SNA = spherical nucleic acid; SNRIs = serotonin and norepinephrine reuptake inhibitor; SSRIs = selective serotonin reuptake inhibitors; tx = treatment; VTEs = venous thromboembolism.

Table 20. Characteristics of ESRs Limited to Perinatal or Older Adult Populations Addressing Harms of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Quality	Outcomes	Population	Intervention	Last search date	Total # of included studies	Total N	Included study designs (Note if conducted IPD analysis)
Gumusoglu, 2022[255]	Fair	Harms, maternal HTN or preeclampsia	Perinatal	SSRIs	Jun-2020	9	1,287,539	Obsrv
KoKoAung, 2015[247]	Good	Harms, Suicide-related	Older adults	SSRIs	Nov-2012	13 (8 RCTs, 5 Obs)	NR	RCTs, Obsrv, QuasiRCT
Krause, 2019[227]	Good	Depression, QoL or functioning, Harms	Older adults	Any pharm	Dec-2017	53	9,274	RCTs
Sobieraj, 2019[252]	Good	Harms	Older adults	SSRIs, SNRIs, bupropion, mirtazapine, trazodone, vilazodone, vortioxetine	May-2018	21 (19 RCTs, 2 obs)	NR	RCTs, Obsrv, QuasiRCT
Viswanathan, 2021[232]	Good	Depression, QoL or functioning, Maternal or fetal, Harms	Perinatal	Any pharm	Jun-2020	164 (10 RCTs, 121 obs in analysis, remaining unadjusted)	NR	RCTs, Obsrv, CCTs
Vlenterie, 2021[257]	Fair	Maternal or fetal,Harms	Perinatal	AD	Jun-2016	27 databases	402,375	No restrictions
Wang, 2018[254]	Good	Harms	Older adults	AD	December-2017	5 (all obs)	53,955	RCTs, Obsrv

Abbreviations: AD = antidepressant; CCTs = controlled clinical trials; ESRs = existing systematic reviews; IPD = individual participant data; N = number of participants; NR = not reported; Obsrv or obs = observation; pharm = pharmacotherapy; QoL = quality of life; QuasiRCT = quasi-randomized controlled trial; RCTs = randomized controlled trials; SNRIs = serotonin and norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

Table 21. Adverse Events Reported in ESRs of Psychological Treatment of Depression (KQ5)

Author, Year	Intervention	Outcome	Population	Control	Followup	k	N analyzed	Effect	ES (95% CI)	I^2 (%)	Narrative summary
Jonsson, 2016[235]	Psychological (any)	Any adverse events	Older adults	Any	NR	14	NR	NR	NR	NR	Safety data were not reported in any included trials
Cuijpers, 2018[197]	Psychological (any)	Deterioration rates	All participants	Any	Post-tx	23	NR	RR	0.39 (0.27 to 0.57)	0	NR
Karyotaki, 2018[236]	Self-guided, iCBT	Deterioration rates	All participants	Any	6-16	13	3,795	OR	0.62 (0.46 to 0.83)	NR	NR
Ebert, 2016[234]	Guided, internet-based intv	Deterioration rates	All participants	Any	26+	4	NR	RR	1.17 (0.49 to 2.87)	0	NR
Ebert, 2016[234]	Guided, internet-based intv	Deterioration rates	All participants	Any	4-17	5	NR	RR	0.47 (0.20 to 1.42)	0	NR
Ebert, 2016[234]	Guided, internet-based intv	Deterioration rates	All participants	Any	Post-tx	21	NR	RR	0.47 (0.29 to 0.75)	0	NR

Abbreviations: CI = confidence interval; ES = evidence synthesis; ESRs = existing systematic reviews; iCBT = internet-based cognitive behavior therapy; intv = intervention; k = number of trials; N = number of participants; NR = not reported; OR = odds ratio; Post-tx = posttreatment; RR = relative risk.

Table 22. Results From Observational Studies of Suicide Attempt Risk With Pharmacologic Treatment for Depression Published After Included ESRs (KQ5)

Author, Year	Study design (Quality)	Country	Study N	Population	Outcome definition	Comparison	Medication	HR (95% CI)*
Valuck, 2016[237]	Retro-spective cohort (Fair)	USA	358,351	General adults with incident depressive episode	Suicide attempt leading to medical encounter	No AD dispensing	SSRI	0.85 (0.17 to 4.19)
							SNRI	0.65 (0.14 to 3.02)
							TCA	0.48 (0.04 to 5.65)
							Multiple AD	2.24 (0.50 to 10.02)

*Demographic covariates included gender; region (East, Midwest, South and West); Medicaid status at time of index depression diagnosis and age at index depression diagnosis; specific and total numbers of mental health comorbidities; specific chronic and acute non-mental health comorbidities; indices of chronic comorbidity including the Chronic Disease Indicator (CDI) score and the Charlson comorbidity score; prior medication use (drug-months of exposure to both psychotropic medications and all prescription medications); use of health services; history of suicide attempt; severity of the index depression diagnosis; physician-level covariates; and a market-level covariate reflecting rates of prescribing of each drug group by generalist vs. specialist prescribers during the month that antidepressant therapy was initiated.

Abbreviations: AD = antidepressant; CI = confidence interval; ESRs = existing systematic reviews; HR = hazard ratio; N = number of participants; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants; USA = United States of America.

Table 23. Characteristics of Anxiety Screening Studies (KQ1)

Author, Year	Quality rating	Study design (Unscreened control?)	Study N	Country	Broad population	Specific population	FUP, wks	Screening approach	Screen pos, %	Condition criteria	Benefit (KQ1)	Harm (KQ3)
Kroenke, 2018[165]	Good	RCT (No)	300	USA	General adults	Primary care patients age ≥18 years screening positive for sleep, pain, anxiety, depression, or fatigue symptoms.	13	Screening results	89	Scored ≥4 (out of 10) on anxiety, depression, sleep, fatigue, or pain sx (single item each)	X	
Mathias, 1994[259]	Fair	Cluster RCT (No)	618	USA	General adults	Primary care patients with elevated anxiety symptoms who were currently unrecognized and untreated.	13, 22	Screening results	7.7	Unrecognized and untreated elevated anxiety symptoms on the SCL-90-R	X	

Abbreviations: FUP = followup; KQ = key question; pos = positive; RCT = randomized controlled trial; SCL-90-R = Symptom Checklist-90-Revised; sx = symptoms; USA = United States of America.

Table 24. Participant Characteristics of Anxiety Screening Studies (KQ1)

Author, Year	Mean age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	% Screen pos	BL MH status
Kroenke, 2018[165]	49.4 (NR)	71.7	High school grad: NR College grad: 13.3	Employed: NR Single: NR Other SES: Edu high school or less: 53.3%	Black: 49.3 Hispanic/Latino: NR Asian/AA: NR Native Am/AN: NR White: 45.0	89	t-score ≥55 on PROMIS depression subscale: 59.3% t-score ≥55 on PROMIS anxiety subscale: 72.3%
Mathias, 1994[259]	42.6 (NR)	58.6	High school grad: NR College grad: 31.7	Employed: NR Single: 20.2 Other SES: Income: 49,000: 23.9%	Black: NR Hispanic/Latino: NR Asian/AA: NR Native Am/AN: NR White: 80.4	7.7	NR

*Non-binary/gender non-conforming categories were not reported in any studies.

Abbreviations: Asian/AA = Asian/Asian American; BL MH = baseline mental health; edu = education; NR = not reported; Native Am/AN = Native American/Alaska Native; pos = positive; PROMIS = Patient-Reported Outcomes Measurement Information System; SES = socioeconomic status.

Table 25. Intervention Characteristics of Anxiety Screening Studies (KQ1)

Author, Year	Target pop	Tng in Screening	Tng in Diagnosis	Tng in treatment	Generic tx guide	Generic handout	Pt-specific tx rec	Referral support	Sx monitoring	Monitoring med use	Med use counseling	PCP Role
Kroenke, 2018[165]	General adults											Deliver most/all of intervention
Mathias, 1994[259]	General adults		X					X				Deliver some of intervention

Abbreviations: Med = medication; NR = not reported; PCP = primary care provider; pop = population; Pt = patient; sx = symptoms; Tng = training; tx = treatment.

Table 26. Results of Anxiety Screening Studies (KQ1)

Author, Year (Pop)	Outcome	Measure	Scale range	Higher score is	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj*
Kroenke, 2018[165] (G)	Depression symptoms	PROMIS-Depression	4-20	Worse	All	IG1	13	151	149	55.8 (10.4)	56 (9.1)	-3.1 (NR)	-1.6 (NR)	-1.5 (NR)	0.174	NR
Mathias, 1994[259] (G)	Anxiety symptoms	GAS	40-81	Worse	All	IG1	22	357	216	60.1 (5.7)	60.8 (5.9)	-2.7 (6.4)	-3.1 (6.5)	0.3 (-1.3 to 2)	0.52	Yes
Kroenke, 2018[165] (G)	Anxiety symptoms	PROMIS-Anxiety	4-20	Worse	All	IG1	13	151	149	59 (10.1)	59.2 (8.7)	-3 (NR)	-2.1 (NR)	-0.8 (NR)	0.471	NR
Mathias, 1994[259] (G)	Global mental health symptoms	GSI	40-81	Worse	All	IG1	22	357	216	63.8 (7.6)	64.6 (7.3)	-3.8 (8.5)	-3.7 (8.7)	-0.1 (-2.3 to 2.1)	0.74	Yes

*Analysis adjusted for baseline values or covariates.

Abbreviations: Adj = adjusted; BL = baseline; Chg = change; CI = confidence interval; CG = control group; Diff = difference; G = general adults; FUP = followup; GAS = Geriatric Anxiety Scale; GSI = Global Severity Index; IG = intervention group; IG1 = intervention group 1; NR = not reported; Pop = population; PROMIS = Patient-Reported Outcomes Measurement Information System; SD = standard deviation; wks = weeks.

Table 27. Characteristics of Studies Examining the Test Accuracy of Instruments to Screen for Anxiety

Author, Year	Quality	Country	Brief population description	N analyzed	Diagnostic interview	Diagnostic criteria	Screening test	Condition
Ahn, 2019[261]	Good	The Republic of Korea	≥19 years, community	1,157	MINI	DSM-IV	GAD-2	Anxiety disorder
								GAD
							GAD-7	Anxiety disorder
								GAD
Austin, 2021[262]	Fair	Australia	Women attending their first prenatal appointment	954	SAGE-SR	DSM-5	GAD-2	Anxiety disorder
							GAD-7	Anxiety disorder
							EPDS - Anxiety Subscale	Anxiety disorder
Gould, 2014[263]	Fair	USA	≥65 years, community-dwelling	110	SCID	DSM-IV	GAS	Anxiety disorder
Kujanpaa, 2014[264]	Fair	Finland	≥18 years, high utilizers of health care	150	MINI	DSM-IV	GAD-2	Anxiety disorder
								GAD
								PD
							GAD-7	Anxiety disorder
								GAD
								PD
Makulowich, 2018[265]	Fair	USA	≥18 years, receiving primary care in an integrated community care clinic	50	MINI	DSM-IV	GAD-7	Anxiety disorder
Matthey, 2013[266]	Fair	Australia	Women attending their first prenatal appointment	249	MINI	DSM-IV	EPDS - Anxiety Subscale	Anxiety disorder
Nath, 2018[267]	Fair	UK	Women using inner-city maternity services	528 (sample without extrapolation)	SCID	DSM-IV	GAD-2	Anxiety disorder
								GAD
Spitzer, 2006[270]	Good	USA	Primary care patients	965	SCID	DSM-IV	GAD-2	Anxiety disorder
								GAD
								PD
								SAnD
							GAD-7	Anxiety disorder
								GAD
								PD
								SAnD

Table 27. Characteristics of Studies Examining the Test Accuracy of Instruments to Screen for Anxiety

Author, Year	Quality	Country	Brief population description	N analyzed	Diagnostic interview	Diagnostic criteria	Screening test	Condition
Spitzer, 1999[269]	Fair	USA	Primary care patients	585	SCID	DSM-III-R	PHQ-PD	PD
Vasiliadis, 2015[271]	Fair	Canada	≥65 years, community-dwelling, attending primary care	1,715	ESA diagnostic module	DSM-IV	GAD-7	Anxiety disorder

Abbreviations: DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EPDS = Edinburgh Postnatal Depression Scale; EPDS-Anxiety subscale = Edinburgh Postnatal Depression Scale - Anxiety subscale; ESA = Enquête sur la Santé des Aînés (Seniors' Health Survey); GAD = Generalized Anxiety Disorder; GAD-2 = generalized anxiety disorder 2-item scale; GAD-7 = generalized anxiety disorder 7-item scale; GAS = Geriatric Anxiety Scale; MINI = Mini International Neuropsychiatric Interview; N = number of participants; PD = panic disorder; PHQ-PD = Patient Health Questionnaire-Panic Disorder; SAGE-SR = Series of Assessments to Guide Evaluation-Self Report; SAnD = social anxiety disorder; SCID = Structured Clinical Interview for DSM Disorders; UK = United Kingdom; USA = United States of America.

Table 28. Participant Characteristics for Studies of Test Accuracy of Anxiety Screening Instrument (KQ2)

Author, Year	N analyzed	Anxiety disorder, n (%)	Mean age, years	Age range, years	% Women*	Race or ethnicity, %	SES
Ahn, 2019[261]	1,157	Any: 218 (18.8) GAD: 90 (7.8)	37	19-85	67	Korean: 100	Mean education, years: 14.6
Austin, 2021[262]	954	Any: 30 (3.1)	34	20-50	100	NR	University education, %: 82
Gould, 2014[263]	110	Any: 10 (9.1) GAD: 2 (1.8)	75	65+	57	White: 90.9	Mean education, years: 17.3
Kujanpaa, 2014[264]	150	Any: 26 (17.3) GAD: 6 (4.0) PD: 10 (6.7)	63	18+	69	NR	Education, % Less than comprehensive school: 10.8 Comprehensive school: 38.5 Matriculation examination: 1.4 Vocational examination: 35.1 College: 13.5 Academic degree: 0.7
Makulowich, 2018[265]	50	Any: 16 (32) GAD: 8 (16)	50	18+	70	White: 26 Black: 8 Asian: 2 Hispanic: 76 Other: 53	NR
Matthey, 2013[266]	249	Any: 35 (14.0)	29	NR	100	NR	Education, % Completed HS: 65.2 Tertiary: 27.6 Recruited from a low-middle SES area of Sydney
Nath, 2018[267]	528 (unextrapolated sample)	Any: 90 (17, weighted) GAD: 79 (15, weighted)	32	14-52	100	White: 53 Black: 32 Asian: 4 Other: 7	Highest education level, % None/school qualifications: 12 College/diploma/higher /certificate/training: 36 Degree level/postgraduate: 52 Income in pounds, % <15,000: 18 15-30,999: 17 31-45,999: 15 46-60,999: 15 >61,000: 35

Table 28. Participant Characteristics for Studies of Test Accuracy of Anxiety Screening Instrument (KQ2)

Author, Year	N analyzed	Anxiety disorder, n (%)	Mean age, years	Age range, years	% Women*	Race or ethnicity, %	SES
Spitzer, 2006[270]	965	Any: 188 (19.5) GAD: 73 (7.6) PD: 66 (6.8) SAnD: 60 (6.2)	47	18-95	65	White: 80 Black: 8 Hispanic: 9	Education, % HS or equivalent: 31 Some college: 62
Spitzer, 1999[269]	585	NR	46†	18-99†	46†	White: 79 Black: 13 Hispanic: 4	Education, % College graduate: 25
Vasiliadis, 2015[271]	1,715	Any: 251 (15.1)	NR	65+	57	NR	NR

*Non-binary/gender non-conforming categories were not reported in any studies.
†These characteristics are from 3,000 patients screened using the full PHQ, not the 585 patients who received the reference standard and used to determine the test accuracy.

Abbreviations: GAD = generalized anxiety disorder; HS = high school; N = number of participants; NR = not reported; PD = panic disorder; SAnD = social anxiety disorder; SES = socioeconomic status.

Table 29. Characteristics of Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Patients (KQ4)

Author, Year	Quality rating	Study design	Study N	Country	Broad population	Specific population	Anxiety required	Disorders	Screen detected	FUP, wks	Intervention	Benefits (KQ4)	Harms (KQ5)
Burger, 2020[274]	Fair	RCT	282	NLD	Perinatal	Adult pregnant individuals with at least moderate anxiety or depression symptoms	No	Anxiety disorder: 30.1 GAD: 22.9 PD: 8.2 SAnD: NR Depressive disorder: 8.2	Yes	g24, g36, p06, p13, p26, p52, p78	IG1: 10-14 individual CBT sessions, delivered in person by licensed psychologists	X	
Clark, 2022[305]	Good	RCT	201	GBR	General adults	Adults, ages 18-65 years with SAnD	Yes	NR: NR GAD: 20 PD: 6 SAnD: 100 MDD: 30	Yes	13, 52	IG1: Up to 14 weekly, 90 min face-to-face therapy sessions plus 3 booster sessions IG2: Personalized internet cognitive therapy program delivered over 14 weeks	X	
Corpas, 2021[275]	Fair	RCT	105	ESP	General adults	Adult patients with mild/ moderate anxiety, depression, or somatoform symptoms meeting one of the following thresholds: GAD-7 ≥5;	No	Anxiety disorder: NR GAD: 63.8 PD: 63.8 SAnD: NR Depressive disorder: 81.9	Yes	8	IG1: 8 one-hour group sessions of transdiagnostic psychotherapy over 8 weeks with psychologist	X	

Table 29. Characteristics of Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Patients (KQ4)

Author, Year	Quality rating	Study design	Study N	Country	Broad population	Specific population	Anxiety required	Disorders	Screen detected	FUP, wks	Intervention	Benefits (KQ4)	Harms (KQ5)
						PHQ-15 ≥5; PHQPD ≥8; PHQ-9 ≥10							
Fletcher, 2005[277]	Fair	RCT	30	GBR	General adults	Primary care patients age ≥16 years with mild to moderate anxiety and/or depression symptoms	No	GAD: NR PD: NR SAnD: NR MDD: NR	No	6, 12	IG1: CBT-oriented self-help manual	X	
Gensichen, 2019[278]	Fair	Cluster RCT	419	DEU	General adults	Adult primary care patients with PD, with or without agoraphobia	Yes	GAD: NR PD: 100 SAnD: MDD: NR	Yes	26, 52	IG1: 4 individual CBT sessions delivered in person, plus case management by general practitioners	X	
Graham, 2020[280]	Good	RCT	146	USA	General adults	Adult primary care patients with symptoms of anxiety or depression	No	Screen positive on GAD-7: 89.7 GAD: NR PD: NR SAnD: NR Screen positive on PHQ-9: 83.6	No	4, 8	IG1: 8-week app-based CBT intervention with one 30- to 45-min orientation phone call, optional 10- to 15-min call mid-treatment, and coaching support via brief text messaging	X	

Table 29. Characteristics of Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Patients (KQ4)

Author, Year	Quality rating	Study design	Study N	Country	Broad population	Specific population	Anxiety required	Disorders	Screen detected	FUP, wks	Intervention	Benefits (KQ4)	Harms (KQ5)
Kendrick, 2005[283]	Fair	RCT	247	GBR	General adults	Primary care patients ages 18-65 years with anxiety or depression symptoms	No	Mixed anxiety disorder and depressive disorder, SAnD, PD, or Agoraphobia: 42.1 GAD: NR PD: 3.6 SAnD: 8.9 Depressive disorder: 33.2	No	8, 26	IG1: One 60-min introductory individual session and five 30- to 45-min individual problem-solving sessions, delivered in person by a community mental health nurse	X	
King, 2000[284]	Fair	RCT	197	GBR	General adults	Adult primary care patients with depression, with or without anxiety	No	Mixed depression and anxiety, PD, or SAnD: 34.7 GAD: NR PD: 3.9 SAnD: 4.8 Depressive disorder: 62.3	No	17, 52	IG1: Up to 12 50-min individual CBT sessions, delivered in person by counselors	X	
Lam, 2010[285]	Fair	RCT	299	HKG	Older adults	Primary care patients age ≥60 years with anxiety or depression symptoms	No	GAD: NR PD: NR SAnD: NR MDD: NR	Yes	6, 12, 26, 52	IG1: Three 20- to 45-min individual problem-solving sessions, delivered in person by a Family Medicine trainee	X	

Table 29. Characteristics of Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Patients (KQ4)

Author, Year	Quality rating	Study design	Study N	Country	Broad population	Specific population	Anxiety required	Disorders	Screen detected	FUP, wks	Intervention	Benefits (KQ4)	Harms (KQ5)
Lang, 2006[286]	Fair	RCT	62	USA	General adults	Adult primary care patients with anxiety or depression symptoms	No	GAD: 32.2 PD: 6.5 SAnD: 14.5 MDD: 67.7	Partial (multiple recruit-ment streams)	0, 4, 17, 30	IG1: One 30- to 60-min individual problem-solving session, delivered in person by a therapist, followed by three 30-to 60-min telephone or in person sessions	X	
Linden, 2005[289]	Fair	RCT	72	DEU	General adults	Adult primary care patients with GAD	Yes	GAD: 100 PD: NR SAnD: NR MDD: NR	No	14.5	IG1: 25 50-min individual CBT sessions, delivered in person by therapists	X	
Nordgren, 2014[290]	Good	RCT	100	SWE	General adults	Adult primary care patients with any anxiety disorder, with or without co-morbid depression	Yes	GAD: 21 PD: 32 SAnD: 45 MDD: NR	No	10	IG1: 7 to 10 modules consisting of text-based guided CBT with therapist support via the internet	X	
O'Mahen, 2022[306]	Fair	RCT	114	GBR	Perinatal	Pregnant individuals experiencing prenatal anxiety	Yes	GAD-7, 7+: 100 GAD: NR PD: NR SAnD: NR MDD: NR	Yes	10, 18, 34	IG1: Three 90-min group sessions over 10 weeks	X	

Table 29. Characteristics of Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Patients (KQ4)

Author, Year	Quality rating	Study design	Study N	Country	Broad population	Specific population	Anxiety required	Disorders	Screen detected	FUP, wks	Intervention	Benefits (KQ4)	Harms (KQ5)
Proudfoot, 2004[292]	Fair	RCT	274	GBR	General adults	Adult primary care patients with any anxiety disorder, mixed anxiety or depression, or depression.	No	Diagnosis of any anxiety disorder: 66.1 GAD: NR PD: 5.1 SAnD: 4.0 Diagnosis of depression: 85.4	Partial (multiple recruit-ment streams)	8, 13, 21, 34	IG1: One 15-min introduction delivered in person, and 8 50-minute computer-based CBT sessions	X	
Rollman, 2018[293]	Good	RCT	704	USA	General adults	Adult primary care patients with at least moderate anxiety symptoms	Yes	GAD: 44.5 PD: 22.7 SAnD: NR MDD: 84.8	No	13, 26, 52	IG1: Internet support group, 8 50-min computerized CBT sessions, and up to 13 15- to 30-min telephone contacts with a care manager	X	
Roy-Byrne, 2010[294]	Good	RCT	1004	USA	General adults	Adult primary care patients with GAD, PD, PTSD, or social anxiety disorder	Yes	GAD: 75.3 PD: 47.3 SAnD: 40.3 MDD: 64.5	Partial (multiple recruit-ment streams)	26, 52, 78	IG1: 6 to 8 individual CBT sessions delivered in person, either alone or with medication by clinical specialist with experience working with anxiety disorders	X	

Table 29. Characteristics of Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Patients (KQ4)

Author, Year	Quality rating	Study design	Study N	Country	Broad population	Specific population	Anxiety required	Disorders	Screen detected	FUP, wks	Intervention	Benefits (KQ4)	Harms (KQ5)
Schreuders, 2007[295]	Fair	RCT	175	NLD	General adults	Adult primary care patients with anxiety or depression symptoms	No	GAD: NR PD: NR SAnD: NR MDD: NR	Yes	13	IG1: 4 to 6 internet-based CBT sessions delivered by nurses	X	
Seekles, 2011[296]	Fair	RCT	120	NLD	General adults	Adult primary care patients with GAD, minor anxiety disorder, PD, social phobia, MDD or dysthymia	No	Any anxiety disorder: 92.6 GAD: NR PD: NR SAnD: NR Depressive disorder: 56.5	Yes	8	IG1: Stepped care program of watchful waiting for 4 weeks, one 30-min orientation session with a psychiatric nurse, 5-week guided self-help problem-solving therapy, and phobia-specific self-help intervention for those with phobias; optional phone or email	X	
Stanley, 2009[298]	Good	RCT	134	USA	Older adults	Patients age ≥60 years with GAD, with or without comorbid MDD, dysthymia or other anxiety disorder	Yes	GAD with or without comorbid depression or other anxiety disorder: 100 GAD: 100 PD: NR SAnD: NR Presence of coexistent	No	26, 39, 52, 65	IG1: Up to 10 individual sessions of CBT delivered in person by a therapist, followed by 4 brief telephone booster sessions	X	

Table 29. Characteristics of Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Patients (KQ4)

Author, Year	Quality rating	Study design	Study N	Country	Broad population	Specific population	Anxiety required	Disorders	Screen detected	FUP, wks	Intervention	Benefits (KQ4)	Harms (KQ5)
								diagnosis of any depression: 44.8					
Stanley, 2014[297]	Fair	RCT	223	USA	Older adults	Primary care patients age ≥60 years with GAD, with or without comorbid MDD, dysthymia or other anxiety disorder	Yes	GAD with or without comorbid depression or other anxiety disorder: 100 GAD: 100 PD: NR SAnD: NR Depressive disorder: 38.6	No	26	IG1: Up to 10 individual CBT sessions, delivered in person or by phone by PhD-level providers	X	
Suchan, 2022[307]	Fair	RCT	63	CAN	Perinatal	Mothers age ≥18 years with postpartum depression or anxiety	No	GAD: NR PD: NR SAnD: NR MDD: NR	Partial (multiple recruit-ment streams)	8, 13	IG1: 8-wk web-based CBT lessons with weekly support from a therapist	X	X
Sundquist, 2015[299]	Fair	RCT	215	SWE	General adults	Adult primary care patients with one or more anxiety disorders, depression, adjustment disorder, or severe stress reaction	No	GAD: NR PD: NR SAnD: NR MDD: NR	No	8	IG1: Eight 2-hr mindfulness-based group therapy sessions, delivered in person	X	
Torres-Platas, 2019[302]	Fair	RCT	61	CAN	Older adults	Patients age ≥60 years with at least moderate anxiety or	No	Anxiety disorder: 57.4 GAD: NR PD: NR	No	8	IG1: 8 2-hr mindfulness-based group sessions, delivered in	X	

Table 29. Characteristics of Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Patients (KQ4)

Author, Year	Quality rating	Study design	Study N	Country	Broad population	Specific population	Anxiety required	Disorders	Screen detected	FUP, wks	Intervention	Benefits (KQ4)	Harms (KQ5)
						depression symptoms		SAnD: NR MDD: 54.1			person by multi-disciplinary care team		
Vera, 2021[304]	Good	RCT	60	USA (PR)	General adults	Spanish-speaking, Hispanic/ Latino primary care patients with scores of at least 5.7 on the GAD-Q-IV and 56 on PSWQ.	Yes	Anxiety disorders: NR GAD: 100 PD: NR SAnD: NR MDD: NR	Yes	20, 28	IG1: Fifteen 1.5-hr individual CBT sessions with a licensed psychologist, delivered weekly for 16 weeks	X	

Abbreviations: CAN = Canada; CBT = cognitive behavioral therapy; DEU = Germany; FUP = followup; GAD = generalized anxiety disorder; GAD-7 = Generalized Anxiety Disorder 7-item scale; GBR = Great Britain; HKG = Hong Kong; IG1 = intervention group 1; KQ = key question; MDD = major depressive disorder; NLD = Netherlands; N = number of participants; NR = not reported; PD = panic disorder; PHQ = Patient Health Questionnaire; PR = Puerto Rico; PSWQ = Penn State Worry Questionnaire; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; SAnD = social anxiety disorder; SWE = Sweden; USA = United States of America.

Table 30. Characteristics of RCTs of Pharmacologic Treatment of Anxiety in Primary Care Patients (KQs 4, 5)

Author, Year	Quality rating	Study design	Study N	Country	Target pop	Population	Anxiety required	Disorders	Screen detected	Followup, wks	Intervention	Benefits	Harms
Lader, 1998[324]	Fair	RCT	246	GBR, FRA	General adults	Primary care patients with GAD and HAM-A score ≥20	Yes	GAD: 100 PD: NR SAnD: NR MDD: 0	NR	4	IG1: Fixed dose of buspirone, 20 mg/day over 4 weeks		X
Lenox-Smith, 2003[287]	Fair	RCT	244	GBR	General adults	Adult primary care patients with GAD	Yes	GAD: 100 PD: NR SAnD: NR MDD: NR	NR	8, 24	IG1: 75-150 mg daily venlafaxine XL for 24 weeks	X	X
Lenze, 2009[288]	Good	RCT	179	USA	Older adults	Individuals age ≥60 years with GAD	Yes	GAD: 100 PD: NR SAnD: NR MDD: 24.9	Partial (multiple recruitment streams)	12	IG1: 12 weeks of 10 mg escitalopram; increased to 20 mg after 4 weeks if no response	X	X

Abbreviations: FRA = France; GAD = generalized anxiety disorder; GBR = Great Britain; HAM-A = Hamilton Rating Scale for Anxiety; IG1 = intervention group 1; MDD = major depressive disorder; N = number of participants; NR = not reported; PD = panic disorder; RCT = randomized controlled trial; SAnD = social anxiety disorder; USA = United States of America.

Table 31. Characteristics of ESRs of Psychological Treatment of Anxiety (KQ4)

Author, Year	Quality	Outcomes	Specific d/o	Population	Intervention	Last Search Date	Total # of Included Studies	Total N	Included Study Designs	Benefits (KQ4)	Harms (KQ5)
van Dis, 2020[321]	Good	Anxiety	None	General population	CBT-specific	Jan-2019	69 Total GAD: 14 PD: 13 SAnD: 7	4,118	RCTs	X	
Hofmann, 2014[317]	Good	QoL or functioning	None	General population	CBT-specific	Feb-2013	59 trials (published in 44 papers)	3,326	NR	X	
Gould, 2012[315]	Good	Depression, Anxiety	None	Older adults	CBT-specific	Nov-2010	12	NR	RCTs	X	
Li, 2022[220]	Good	Depression, Anxiety	None	Perinatal	CBT-specific	Apr-2020	77 (68 in MA)	11,221	RCTs, QuasiRCT	~~X~~	
Ponting, 2020[211]	Good	Depression	None	Perinatal Black and Hispanic/Latino	Psychological	Sep-2018	13 (10 RCTs)	1,971	RCTs, CCTs	X	
Weaver, 2017[215]	Good	Depression, Anxiety	None	Rural settings	CBT-specific	Apr-2015	16	1,193	No restrictions	X	
Cuijpers, 2016[313]	Good	Anxiety	GAD, SAnD, PD	General population	CBT-specific	Aug-2015	144 Total (184 comparisons) GAD: 24 PD: 30 SAnD: 36 (Comparisons: 31 for GAD, 42 for PD, and 48 for SAnD)	11,030	RCTs	X	
Cuijpers, 2016[313]	Good	Depression	GAD, SAnD, PD	General population	CBT-specific	Aug-2015	81 total GAD: 16 SAnD: 13 PD: 18 MDD: 34	5,486	RCTs	X	

Abbreviations: CBT = cognitive behavioral therapy; CBT-specific = cognitive behavioral therapy-specific; CCTs = controlled clinical trials; ESRs = existing systematic reviews; GAD = generalized anxiety disorder; IPD = individual participant data; NR = not reported; MA = meta-analysis; PD = panic disorder; QoL = quality of life; QuasiRCT = quasi-randomized controlled trial; RCTs = randomized controlled trials; SAnD = social anxiety disorder.

Table 32. Characteristics of ESRs of Pharmacologic Treatment of Anxiety (KQs 4, 5)

Author, Year	Quality	Outcomes	Specific d/o	Population	Intervention	Last Search Date	Total # of Included Studies	Total N	Included Study Designs (Note if conducted IPD analysis)	Benefits (KQ4)	Harms (KQ5)
Balasubramaniam, 2019[309]	Good	Anxiety, Harms	None	Older adults	AD	Oct-2018	12	NR	RCTs	X	X
Bighelli, 2018[310]	Good	Anxiety, Harms	PD	General population	AD	May-2017	47	9,377	RCTs	X	X
Breilmann, 2019[311]	Good	Anxiety, Harms	PD	General population	BZD	May-2018	23	4,233	RCTs	X	X
Chen, 2019[312]	Good	Anxiety	GAD	General population	Any pharm	Sep-2017	91	15,596	RCTs	X	
Gupta, 2020[316]	Good	Anxiety, Harms	None	Older adults	BZD	Aug-2018	5	553	RCTs	X	X
Imai, 2014[318]	Good	Anxiety, Harms	PD	General population	Anxiolytics	Jan-2014	3	170	RCTs, Randomized cross-over trials	X	X
Roest, 2015[319]	Fair	Anxiety	None	General population	2nd-gen AD	Dec-2012	57	NR	RCTs	X	
Slee, 2019[320]	Good	Anxiety, Harms	GAD	General population	Any pharm	Aug-2017	89	25,441	RCTs	X	X
Viswanathan, 2021[232]	Good	Depression, QoL or functioning, Maternal or fetal, Harms	None	Perinatal	Any pharm	Jun-2020	164	NR	RCTs, Obsrv, CCTs	X	X
Williams, 2017[322]	Good	Depression, Anxiety, QoL or functioning, Harms	SAnD	General population	Any pharm	Aug-2015	66	11,597	RCTs	X	X

Abbreviations: AD = antidepressant; BZD = benzodiazepines; CCTs = controlled clinical trials; ESRs = existing systematic reviews; GAD = generalized anxiety disorder; IPD = individual participant data; NR = not reported; Obsrv = observation; PD = panic disorder; pharm = pharmacotherapy; QoL = quality of life; RCTs = randomized controlled trials; SAnD = social anxiety disorder.

Table 33. Summary of Meta-Analysis Results for Anxiety Outcomes in Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Patients (KQ4)

Outcome	No. studies (n analyzed)	Type of effect	Pooled result (95% CI)*	I^2, %	Tau^2	Range of effects (in native units)†	Median (IQR) effects†
Anxiety symptom severity							
All studies	22 (3,943)	SMD	-0.29 (-0.44 to -0.15)	70.6	0.06	-8.0 to 6.8	-1.8 (-2.8 to -0.5)
Anxiety required	10 (2,075)	SMD	-0.41 (-0.58 to -0.23)	40.2	0.02	-8.0 to 6.8	-2.3 (-3.0 to -1.4)
Anxiety or depression	12 (1,868)	SMD	-0.18 (-0.39 to 0.03)	66.7	0.06	-6.1 to 4.5	-0.7 (-2.4 to 0.4)
Depression symptom severity							
All studies	22 (3,970)	SMD	-0.32 (-0.46 to -0.19)	66.4	0.05	-9.0 to 6.3	-1.50 (-2.6 to 0.01)
Anxiety required	9 (1,990)	SMD	-0.49 (-0.74 to -0.25)	68.4	0.05	-9.0 to 6.3	-2.0 (-2.7 to -1.5)
Anxiety or depression	13 (1,980)	SMD	-0.20 (-0.34 to -0.06)	39.9	0.02	-6.5 to 4.4	-0.7 (-2.4 to 0.01)
Mental Components Score	7 (2,104)	SMD	0.17 (-0.03 to 0.36)	54.4	0.02	-5.4 to 9.8	0.4 (-1.3 to 3.5)
Physical Component Score	5 (1,656)	SMD	0.03 (-0.12 to 0.18)	13.0	0.0	-1.5 to 2.2	0.3 (-1.5 to 0.6)

*Effect based on restricted maximum likelihood model with the Knapp-Hartung adjustment for small samples.
†Range of effects for all study arms, subgroup analyses, and timepoints (i.e., not limited to records in the meta-analysis).

Abbreviations: CI = confidence interval; IQR = interquartile range; SMD = standardized mean difference.

Table 34. Summary of Participant Demographic Characteristics in Primary Studies of Psychological Treatment of Anxiety in Primary Care Patients (KQ4); Weighted Mean (Number of Studies Reporting), Unless Otherwise Indicated

Population	No. of studies (No. US-based studies)	Total N	Mean age	% Women*	Race or ethnicity (US-based studies only), %	Race or ethnicity, range of % of participants among US-based studies
All	24 (7)	5,208	45.4 (24)	74.5 (24)	Black: 15.3 (6) Asian-Amer/PI: 1.50 (3) Native Amer/AN: 0.64 (2) Hispanic/Latino: 16.3 (5) White: 68.5 (6)	Black: 8 to 32 Asian-Amer/PI: 1 to 2.2 Native Amer/AN: 0.4 to 1 Hispanic/Latino: 7 to 24 White: 56.6 to 81.8
Older	4 (2)	717	69.1 (4)	61.9 (4)	Black: 18.2 (2) Asian-Amer/PI: 1.7 (2) Native Amer/AN: 0.4 (1) Hispanic/Latino: 9.82 (2) White: 75.6 (2)	Black: 17.9 to 18.7 Asian-Amer/PI: 1.4 to 2.2 Native Amer/AN: 0.4 to 0.4 Hispanic/Latino: 8.2 to 10.8 White: 70.2 to 78.9
Perinatal	3 (0)	459	32.2 (3)	100 (0)	NA	NA

*Gender was not reported in studies of perinatal patients so participants are counted as women, recognizing that there may be some individuals who do not identify as women; non-binary/gender non-conforming categories were not reported in any studies.

Abbreviations: Asian-Amer/PI = Asian American/Pacific Islander; N = number of participants; Native Am/AN = Native American/Alaska Native; NR = not reported; US = United States.

Table 35. Summary of Intervention Components in Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Patients (KQ4)

Anxiety required	Author, Year	IG	Duration, wks	Therapeutic approach	Est contact hrs	Delivery	PC Team role	Control
Yes	Clark, 2022[305]	IG1	14	CBT	25.5	In-person	None	Waitlist
Yes	Clark, 2022[305]	IG2	14	CBT	NA	Phone, Web, Email or Text	None	Waitlist
Yes	Gensichen, 2019[278]	IG1	23	CBT	2	In-person, Print	Most/all	Usual care
Yes	Linden, 2005[289]	IG1	14	CBT	5.8	In-person	None	Waitlist
Yes	Nordgren, 2014[290]	IG1	10	CBT	NA	Web, Virtual	None	Attention Control
Yes	O'Mahen, 2022[306]	IG1	10	CBT	4.5	In-person	None	Usual specialty mental health care
Yes	Rollman, 2018[293]	IG1	26	CBT	10.8	Phone, Web, Email or Text	None	Usual care
Yes	Rollman, 2018[293]	IG2	26	CBT, Support group	10.8	Phone, Web, Email or Text	None	Usual care
Yes	Roy-Byrne, 2010[294]	IG1	11	CBT	NR	In-person	None	Usual care
Yes	Stanley, 2009[298]	IG1	12	CBT	5.3	In-person, Phone	None	Minimal
Yes	Stanley, 2014[297]	IG1	26	CBT	5	In-person, Phone	None	Usual care
Yes	Vera, 2021[304]	IG1	16	CBT	22.5	In-person	None	Usual care
No	Burger, 2020[274]	IG1	33	CBT	NR	In-person	None	Usual care
No	Corpas, 2021[275]	IG1	8	CBT	8	In-person	None	Usual care
No	Fletcher, 2005[277]	IG1	12	CBT	NA	Print	None	Waitlist
No	Graham, 2020[280]	IG1	8	CBT	0.8	Phone, Web, Email or Text	None	Waitlist
No	Kendrick, 2005[283]	IG1	8	Problem-Solving Therapy	3.5	In-person	None	Usual care
No	Kendrick, 2005[283]	IG2	8	NR	3.5	In-person	None	Usual care
No	King, 2000[284]	IG1	NR	CBT	5	In-person	None	Usual care
No	King, 2000[284]	IG2	NR	Non-directive	5	In-person	Some	Usual care
No	Lam, 2010[285]	IG1	5	Problem-Solving Therapy	1.5	In-person	None	Minimal

Table 35. Summary of Intervention Components in Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Patients (KQ4)

Anxiety required	Author, Year	IG	Duration, wks	Therapeutic approach	Est contact hrs	Delivery	PC Team role	Control
No	Lang, 2006[286]	IG1	NR	Problem-Solving Therapy	3	In-person, Phone	None	Usual care
No	Proudfoot, 2004[292]	IG1	9	CBT	6.9	Web	None	Usual care
No	Schreuders, 2007[295]	IG1	NR	CBT	3	Web	None	Usual care
No	Seekles, 2011[296]	IG1	8	Problem-Solving Therapy, Case Mgmt	NR	In-person, Web, Email or Text	None	Usual care
No	Suchan, 2022[307]	IG1	8	CBT	NR	Phone, Web, Email or Text	None	Usual care
No	Sundquist, 2015[299]	IG1	8	Mindful	16	In-person	None	Usual care
No	Torres-Platas, 2019[302]	IG1	8	Mindful	16	In-person	None	Usual care

Abbreviations: CBT = cognitive behavioral therapy; Est = estimated; IG = intervention group; IG1 = intervention group 1; IG2 = intervention group 2; Mgmt = management; NA = not applicable; NR = not reported; PC = primary care.

Table 36. Participant Characteristics of Primary Research Studies of Pharmacologic Treatment of Anxiety in Primary Care Patients (KQ4)

Author, Year	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	BL MH status
Lenox-Smith, 2003[287]	47 (19-79)	59.0	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: NR	Black: NR Hispanic/Latino: NR Asian/AA: NR Native Am/AN: NR White: NR	NR
Lenze, 2009[288]	71.7 (60+)	61.3	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: Edu (yrs, mean): 13.9	Black: NR Hispanic/Latino: NR Asian/AA: NR Native Am/AN: NR White: 82.5	MDD: 24.9% GAD: 100% Exception: 14.7% Benzodiazepine: 0%

*Gender was not reported in studies of perinatal patients so participants are counted as women, recognizing that there may be some individuals who do not identify as women; non-binary/gender non-conforming categories were not reported in any studies.

Abbreviations: Asian/AA = Asian/Asian American; BL MH = baseline mental health; Edu = education; GAD = generalized anxiety disorder; MDD = major depressive disorder; Native Am/AN = Native American/Alaska Native; NR = not reported; SES = socioeconomic status.

Table 37. Adverse Outcomes Reported in Primary Research Studies of Pharmacologic Treatment of Anxiety in Primary Care Patients (KQ5)

Author, Year	Medication	Serious Adverse Events, N (%)		Any Adverse Events, N (%)		Dropout Due to Adverse Events, N (%)		Most Common Nonserious AEs
-	-	Medication	Placebo	Medication	Placebo	Medication	Placebo	-
Lenze, 2009[288]	Escitalopram	0	0	65 (76)	59 (64)	3 (4)	4 (4)	Fatigue or somnolence, sleep disturbance, urinary sx
Lenox-Smith, 2003[287]	Venlafaxine XL	4 (3.3)	5 (4.1)	112 (92)	110 (90)	NR	NR	NR
Lader, 1998[324]	Buspirone	0	0	31 (38)	23 (28)	NR	NR	Headache, dizziness

Abbreviations: AEs = adverse events; N = number of participants; NR = not reported; sx = symptoms; XL = extended release.

Table 38. Characteristics of ESRs Addressing Harms of Pharmacologic Treatment of Anxiety (KQ5)

Author, Year	Quality	Outcomes	Population	Intervention	Last Search Date	Total # of Included Studies	Total N	Included Study Designs (Note if Conducted IPD Analysis)
Balasubramaniam, 2019[309]	Good	Anxiety, Harms	Older adults	AD	Oct-2018	12	NR	RCTs
Bighelli, 2018[310]	Good	Anxiety, Harms	General population	AD	May-2017	47	9,377	RCTs
Breilmann, 2019[311]	Good	Anxiety, Harms	General population	BZD	May-2018	23	4,233	RCTs
Gupta, 2020[316]	Good	Anxiety, Harms	Older adults	BZD	Aug-2018	5	553	RCTs
Imai, 2014[318]	Good	Anxiety Harms	General population	Anxiolytics	Jan-2014	3	170	RCTs, Randomized cross-over trials
Jensen, 2019[244]	Good	Harms	General population	SSRIs	Dec-2017	30	>845,655	RCTs, Obsrv
Khanassov, 2018[246]	Good	Harms	General population	SSRIs and SNRIs	Nov-2016	33	NR	Obsrv
Kunutsor, 2018[248]	Good	Harms	General population	AD	Apr-2018	8	960,113 (9,027 VTEs)	Obsrv
Maslej, 2017[249]	Good	Harms	General population	AD	Jun-2014	16	378,400	RCTs, Obsrv
Na, 2018[250]	Good	Harms	General population	Bupropion, Mirtazapine	May-2017	7	NR	Obsrv
Slee, 2019[320]	Good	Anxiety, Harms	General population	Any pharm	Aug-2017	89	25,441	RCTs
Trajkova, 2019[253]	Good	Harms	General population	AD	Sep-2018	31	NR	Obsrv
Viswanathan, 2021[232]	Good	Depression, Anxiety, QoL or functioning, Maternal or fetal, Harms	Perinatal	Any pharm	Jun-2020	164	NR	RCTs, Obsrv, CCTs
Wang, 2018[254]	Good	Harms	Older adults	AD	December-2017	5	53,955	RCTs, Obsrv

Table 38. Characteristics of ESRs Addressing Harms of Pharmacologic Treatment of Anxiety (KQ5)

Author, Year	Quality	Outcomes	Population	Intervention	Last Search Date	Total # of Included Studies	Total N	Included Study Designs (Note if Conducted IPD Analysis)
Williams, 2017[322]	Good	Depression, Anxiety, QoL or functioning, Harms	General population	Any pharm	Aug-2015	66	11,597	RCTs

Abbreviations: AD = antidepressant; BZD = benzodiazepines; CCTs = controlled clinical trials; ESRs = existing systematic reviews; IPD = individual participant data; N = number of participants; NR = not reported; Obsrv = observation; pharm = pharmacotherapy; QoL = quality of life; RCTs = randomized controlled trials; SNRIs = serotonin and norepinephrine reuptake inhibitor; SSRIs = selective serotonin reuptake inhibitors; VTE = venous thromboembolism.

Table 39. Observational Studies of Harms of Pharmacologic Treatment of Anxiety, Excluding Antidepressant Treatment (KQ5)

Author, Year	Study design (Quality)	Country	Study N	Population	Exposure	Outcome	Matching variables	OR (95% CI)
Cato, 2019[325]	Case-control (Fair)	SWE	308	General adults	Benzodiazepine (prescription)	Suicide death	Age, sex, psychiatric diagnosis, and mental health treatment in the same timeframe (1:1 matching)	1.83 (1.06 to 3.14)*
Sheehy, 2019[326]	Case-control (Good)	CAN	262,070	Pregnant	Benzodiazepine (dispensing)	Spontaneous abortion, gestational weeks 6-20	Gestational age and calendar year (1:5 matching)	1.85 (1.61 to 2.12)† *Statistically significant effects for both long- and short-acting agents, and all specific agents. Dose-response effect was also identified.*

*Adjusted for prescription for antidepressant, anticonvulsant, lithium, psychostimulant, antipsychotics, sedatives; previous suicide attempt; previous inpatient psychiatric care; previous inpatient somatic care; age; sex; 9 mental health diagnosis categories (depressive, anxiety, aspergers/ADHD, etc.).
†Adjusted for antidepressant use, antipsychotic use, maternal age, welfare recipient, urban dweller, past 12 month healthcare utilization (inpatient, general practitioner, psychiatric, other specialty), past 12 month mental health diagnosis (mood and anxiety disorder, insomnia), folic acid exposure, medical comorbidities (hypertension, diabetes, asthma, thyroid disorders, tobacco, alcohol or other drug dependence), and other pregnancy in previous 12 months.

Abbreviations: CAN = Canada; CI = confidence interval; N = number of participants; OR = odds ratio; SWE = Sweden.

Table 40. Characteristics of Suicide Risk Screening Studies (KQ1)

Author, Year	Quality rating	Study Design (Unscreened Control?)	Study N	Country	Broad Population	Specific Population	FUP, wks	Screening Approach	Screen Pos, %	Condition Criteria	Benefit (KQ1)	Harm (KQ3)
Crawford, 2011[327]	Fair	RCT (Yes)	443	GBR	General adults	Adults answering "Yes" to either of two depression screening items	2	Screening	NR	"Yes" on either of two depression screening items	X	X

Abbreviations: FUP = followup; GBR = Great Britain; KQ = key question; N = number of participants; NR = not reported; Pos = positive; RCT = randomized controlled trial.

Table 41. Participant Characteristics of Suicide Risk Screening Studies (KQ1)

Author, Year	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	% Screen Pos	BL MH status
Crawford, 2011[327]	48.5 (16-92)	69.1	High school grad: NR College grad: Completed higher education, 33.0%	Employed: 47.7 Single: 56.9 Other SES: NR	Black: NR Hispanic/Latino: NR Asian/AA: NR Native Am/AN: NR White: NR	NR	"Yes" on either of 2-item screening questionnaire: 100%

*Non-binary/gender non-conforming categories were not reported.

Abbreviations: Asian/AA = Asian/Asian American; BL MH = baseline mental health; Native Am/AN = Native American/Alaska Native; NR = not reported; Pos = positive; SES = socioeconomic status.

Table 42. Intervention Characteristics of Suicide Risk Screening Studies (KQ1)

Author, Year	Target Pop	Tng in Screening	Tng in Diagnosis	Tng in Treatment	Generic tx Guide	Generic Handout	Pt-Specific tx Rec	Referral Support	Sx Monitoring	Monitoring Med Use	Med Use Counseling	PCP Role
Crawford, 2011[327]	General adults	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Not involved

Abbreviations: Med = medication; NR = not reported; PCP = primary care provider; Pop = population; Pt = patient; Rec = recommendation; sx = symptoms; Tng = training; tx = treatment.

Table 43. Results From Suicide Risk Screening Studies (KQ1)

Author, Year (Pop)	Outcome	Measure	IG	Analyzed	FUP, wks	OR (95% CI)	IG n/N (%)	CG n/N (%)	p-value	Adjusted
Crawford, 2011[327] (G)	Suicide attempt	Suicide attempt	IG1	All	2	0.38 (0.02 to 9.34)	0/164 (0.0)	1/187 (0.5)	NR	No
Crawford, 2011[327] (G)	Suicidal ideation	Felt life not worth living	IG1	All	2	1.23 (0.76 to 1.98)	46/164 (28.0)	45/187 (24.1)	NR	Yes
Crawford, 2011[327] (G)	Suicidal ideation	Thought of taking own life	IG1	All	2	1.36 (0.72 to 2.54)	24/164 (14.7)	21/187 (11.3)	NR	Yes
Crawford, 2011[327] (G)	Suicidal ideation	Wished to be dead	IG1	All	2	1.01 (0.61 to 1.66)	38/164 (23.2)	43/187 (22.9)	NR	Yes

Abbreviations: CI = confidence interval; CG = control group; FUP = followup; G = general adults; IG = intervention group; IG1 = intervention group 1; NR = not reported; OR = odds ratio; Pop = population.

Table 44. Characteristics of Studies Examining Test Accuracy of Suicide Risk Screening Instruments to Identify People at Increased Risk of Suicide (KQ2)

Author, Year	Quality	Country	Brief population description	N analyzed	Diagnostic interview	Screening test
Desjardins, 2016[328]	Fair	USA	Age ≥18 years from the ED with any chief complaint	124	Unstructured interview from a psychiatrist	Suicide Risk Assessment Tool
Heisel, 2010[329]	Fair	USA	Age ≥65 years from primary care	626	SCID and Ham-D	GDS-15
						GDS-SI
Olfson, 1996[330]	Fair	USA	Ages 18-70 years	1,001	SCID	SDDS-PC - Feeling suicidal
						SDDS-PC - Thoughts of death
						SDDS-PC - Wishing you were dead

Abbreviations: ED = emergency department; GDS = Geriatric Depression Scale; GDS-SI = Geriatric Depression Scale – Suicide Ideation; HAM-D = Hamilton Rating Scale for Depression; N = number of participants; SCID = Structured Clinical Interview for DSM Disorders; SDDS-PC = Symptom Driven Diagnostic System for Primary Care; USA = United States of America.

Table 45. Participant Characteristics for Studies of Test Accuracy of Suicide Risk Screening Instruments (KQ2)

Author, Year	N	Suicide Risk, n/n (%)	Mean Age	Age Range	% Women*	Race or Ethnicity, %	SES
Heisel, 2010[329]	626	69/626 (11)	75	65-95	62	White: 93 Black: 5 Other: 2	Mean years of education: 14 Employment Status, % Retired: 82 Unemployed/disability benefits: 2 Part/Full-time employment: 14 Part/Full-time student: <1
Olfson, 1996[330]	1,001	12/1,001 (1.2)	49	18-70	63	NR	NR
Desjardins, 2016[328]	124	3/124 (2.4)	47	≥18	50	NR	NR

*Non-binary/gender non-conforming categories were not reported in any studies.

Abbreviations: N = number of participants; NR = not reported; SES = socioeconomic status.

Table 46. Characteristics of Suicide Prevention Studies (KQ4)

Author, Year	Quality rating	Study design	Study N	Country	Target pop	Population	Followup, wks	Intervention	Benefits	Harms
Borschmann, 2013[336]	Good	RCT	88	GBR	General adults	Adults with borderline personality disorder and self-harm in the past 12 months	26	IG1: One 60-min joint crisis plan meeting.	X	X
Bruce, 2004[337]	Fair	Cluster RCT	598	USA	Older adults	Adults age ≥60 years with MDD or minor depressive disorder	16, 35, 52	IG1: Individually tailored in-person or phone-based depression care management.	X	
Bush, 2017[338]	Good	RCT	118	USA	General adults	Veterans in mental health treatment expressing suicidal ideation	3, 6, 12	IG1: App-based CBT intervention.	X	
Carter, 2010[340]	Fair	RCT	76	AUS	General adults	Adult women, ages 18-65 years, with borderline personality disorder and a history of self-harm	13, 26	IG1: Individual (number NR) and 24 group DBT sessions, and phone calls (number NR) with individual therapist.	X	
Davidson, 2006[342]	Good	RCT	106	GBR	General adults	Patients with borderline personality disorder and self-harm in previous 12 months	52, 104	IG1: Up to 30 60-min CBT sessions	X	
Franklin, 2016[343]	Fair	RCT	163	USA	General adults	Adults recruited from online mental health forums reporting at least one suicidal behavior within the past year	4	IG1: Mobile game-like app called Therapeutic Evaluative Conditioning (TEC), designed to increase aversion to self-injurious thoughts and behaviors and	X	

Table 46. Characteristics of Suicide Prevention Studies (KQ4)

Author, Year	Quality rating	Study design	Study N	Country	Target pop	Population	Followup, wks	Intervention	Benefits	Harms
								decrease aversion to the self.		
Goodman, 2016[345]	Fair	RCT	91	USA	General adults	Veterans ages 18-55 years at high risk of suicide	12, 26, 52	IG1: 26 50- to 60-min individual and 26 90-min group DBT sessions.	X	
Jobes, 2017[347]	Fair	RCT	148	USA	General adults	Active-duty US Army soldiers, age ≥18 years with significant suicidal ideation (≥13 on SSI-C)	4, 13, 26, 52	IG1: ≥4 counseling sessions based on CAMS approach.	X	
Katz, 2022[362]	Fair	RCT	519	USA	General adults	Veterans with depression or bipolar disorder who had survived a recent suicidal event	8.5, 52	IG1: Lithium 600 mg/d for 1 year plus usual VA mental health care	X	X
Kovac, 2002[348]	Fair	RCT	121	USA	General adults	College students age ≥18 years who screened positive for increased risk of suicide	2, 6	IG1: Four 20-min writing sessions over 2 weeks about thoughts and feelings associated with the most difficult time(s) in their life.	X	
Linehan, 2006[349]	Fair	RCT	111	USA	General adults	Women ages 18-45 years with borderline personality disorder and recent self-harm	52, 104	IG1: 52 1-hr individual and 52 2.5-hr group DBT sessions, plus telephone consultation as needed.	X	
McMain, 2017[350]	Fair	RCT	84	CAN	General adults	Adults ages 18-60 years with borderline personality disorder and recent history of	10, 20, 32	IG1: 20 2-hour DBT skills training group sessions.	X	

Table 46. Characteristics of Suicide Prevention Studies (KQ4)

Author, Year	Quality rating	Study design	Study N	Country	Target pop	Population	Followup, wks	Intervention	Benefits	Harms
						suicidal and/or NSSI episodes.				
Mühlmann, 2021[351]	Fair	RCT	402	DNK	General adults	Adults age ≥18 years in Denmark with suicidal thoughts	6, 32	IG1: Six online self-help CBT modules, available over 6 weeks.	X	
Pigeon, 2019[353]	Good	RCT	54	USA	General adults	Veterans ages 18-70 years who screened positive for suicidal ideation, insomnia, and co-occurring PTSD and/or depression.	6	IG1: Four individual sessions of brief CBT for insomnia with a behavioral health provider.	X	
Pistorello, 2012[354]	Fair	RCT	63	USA	General adults	College students experiencing suicidal ideation with a history of self-harm and characteristics of borderline personality disorder	12, 26, 38, 52, 78	IG1: 52 50-min individual and 52 90-min DBT group sessions, additional coaching as needed.	X	
Pistorello, 2021[363]	Fair	RCT	62	USA	General adults	College students seeking services at a college counseling center and at risk for suicide	13	IG1: 4 to 8 weekly CAMS therapy sessions.	X	
Priebe, 2012[355]	Fair	RCT	80	GBR	General adults	Patients with borderline personality disorder and recent self-harm	52	IG1: 52 1-hour individual and 52 2-hour DBT group sessions, telephone coaching as needed.	X	

Table 46. Characteristics of Suicide Prevention Studies (KQ4)

Author, Year	Quality rating	Study design	Study N	Country	Target pop	Population	Followup, wks	Intervention	Benefits	Harms
Riblet, 2022[364]	Fair	RCT	20	USA	General adults	Primary care veteran patients at risk for suicide	4, 13	IG1: Educational materials, 1-hour phone or video educational session followed by 6 additional contacts over 3 months; focus on symptom monitoring, safety planning, treatment adherence.	X	
Simon, 2022[365]	Good	RCT	18882	USA	General adults	Adult outpatients who report recent frequent suicidal thoughts (PHQ-9 item 9=2-3)	78	IG1: Structured care management program, including a series of patient outreach contacts over 12 months. IG2: 4-session online skills training program supported by messages from skills coach to support program engagement, offered for up to 12 months.	X	
Torok, 2022[366]	Fair	RCT	455	AUS	General adults	Young adults (ages 18-25 years) at risk of suicide	6	IG1: LifeBuoy: a brief, self-guided DBT smartphone application with 7 modules delivered over 6 weeks.	X	
Van Orden, 2021[359]	Fair	RCT	62	USA	Older adults	Adults, age ≥60 years, reported subjective disconnection (feeling lonely	3, 6, 10	IG1: Up to 10 in-home individual social activation intervention sessions over	X	

Table 46. Characteristics of Suicide Prevention Studies (KQ4)

Author, Year	Quality rating	Study design	Study N	Country	Target pop	Population	Followup, wks	Intervention	Benefits	Harms
						and/or like a burden)		approximately 10 weeks.		
van Spijker, 2014[358]	Good	RCT	236	NLD	General adults	Adults age ≥18 years scoring between 1 and 26 on Beck Scale for Suicide Ideation (BSS)	2, 4, 6	IG1: 6-week online CBT educational modules with automated email followup.	X	
Ward-Ciesielski, 2017[361]	Fair	RCT	93	USA	General adults	Adults age ≥18 years with suicidal ideation in the past week and no mental health treatment in the past month	1, 4, 12	IG1: One 45- to 60-min DBT session.	X	

Abbreviations: AUS = Australia; CAMS = Collaborative Assessment and Management of Suicidality; CAN = Canada; CBT = cognitive behavioral therapy; DBT = dialectical behavior therapy; GBR = Great Britain; IG1 = intervention group 1; MDD = major depressive disorder; NLD = Netherlands; NR = not reported; NSSI = non-suicidal self-injury; pop = population; PHQ = Patient Health Questionnaire; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; SSI-C = Scale for Suicide Ideation--Current; USA = United States of America.

Table 47. Summary of Meta-Analysis Results for Suicide Prevention Studies (KQ4)

Outcome	No. studies (n analyzed)	Type of effect	Pooled result (95% CI)*	I^2, %	Tau^2	Range of effects†	Median (IQR) effects†
% With suicide attempt	12 (14,573)	OR	0.94 (0.73 to 1.22)	11.2	0.02	0.34 to 4.59 ARD: -23.6 to +8.3 percentage points	0.94 (0.61 to 1.05) ARD: 0.0 (-2.6 to +0.5) percentage points
Suicidal ideation (continuous measures)	12 (1,734)	SMD	-0.14 (-0.31 to 0.02)	54.8	0.04	Mean diff in change: -11.8 to +5.2	Mean diff in change: -0.7 (-2.5 to +0.2)
Depression symptoms severity	11 (2,177)	SMD	-0.22 (-0.33 to -0.10)	0	0	-12.8 to +2.5	-1.8 (-3.2 to -0.3)

*Effect based on restricted maximum likelihood model with the Knapp-Hartung adjustment for small samples.
†Range of effects for all study arms, subgroup analyses, and timepoints (i.e., not limited to records in the meta-analysis).

Abbreviations: ARD = absolute risk difference; CI = confidence interval; diff = difference; IQR = interquartile range; OR = odds ratio; SMD = standardized mean difference.

Table 48. Summary of Participant Demographic Characteristics Among Studies of Suicide Prevention (KQ4); Weighted Mean (Number of Studies Reporting), Unless Otherwise Indicated

Condition	No. of studies (no. US-based studies)	Total N	Mean age	% Women*	Race or ethnicity (US-based studies only)	Race or ethnicity, range of % of participants among US-based studies
Suicide	23 (15)	22,632	33.8 (21)	66.3 (22)	Black: 4.7 (12) Asian-Amer/PI: 3.4 (9) Native Amer/AN: 0.8 (7) Hispanic/Latino: 8.7 (10) White: 74.3 (14)	Black: 1.8 to 31.9 Asian-Amer/PI: 1 to 16.1 Native Amer/AN: 0.7 to 4.8 Hispanic/Latino: 3.6 to 45.1 White: 14.3 to 92

*Gender was not reported in studies of perinatal patients so participants are counted as women, recognizing that there may be some individuals who do not identify as women; non-binary/gender non-conforming categories were not reported in any studies.

Abbreviations: Asian-Amer/PI = Asian American/Pacific Islander; N = number of participants; Native Am/AN = Native American/Alaska Native; US = United States.

Table 49. Intervention Characteristics of Suicide Prevention Studies (KQ4)

Author, Year	IG	Duration, wks	Therapeutic Approach	Est Contact Hours	Delivery	PC Team Role	Control
Borschmann, 2013[336]	IG1	0.14	Other	1	In-person	None	Usual care
Bruce, 2004[337]	IG1	NR	Care management		In-person, Phone	Some	Usual care
Bush, 2017[338]	IG1	12	CBT	NR	Web	None	Enhanced usual care
Carter, 2010[340]	IG1	26	DBT	24	In-person, Phone	None	Usual care
Davidson, 2006[342]	IG1	52	CBT	3	In-person	None	Usual care
Franklin, 2016[343]	IG1	4	Other	NR	Virtual	None	Usual care
Goodman, 2016[345]	IG1	26	DBT	62.8	In-person, Phone	None	Usual care
Jobes, 2017[347]	IG1	4-52	Other	2.5	In-person	None	Enhanced usual specialty MH care
Katz, 2022 #41302	IG1	52	Lithium	NA	NA	Most/all	Placebo
Kovac, 2002[348]	IG1	2	Other	1.3	In-person	None	Minimal
Linehan, 2006[349]	IG1	52	DBT	182	In-person, Phone	None	Enhanced usual specialty MH care
McMain, 2017[350]	IG1	20	DBT	41.5	In-person	None	Waitlist
Mühlmann, 2021[351]	IG1	6	CBT	NR	Web	None	Waitlist
Pigeon, 2019[353]	IG1	6	CBT	1	In-person	None	Usual care
Pistorello, 2012[354]	IG1	52	DBT	121.3	In-person, Phone	None	Enhanced usual specialty MH care
Pistorello, 2021 #42286	IG1	4-8	CAMS	8	In-person	None	Usual specialty MH care
Priebe, 2012[355]	IG1	52	DBT	156	In-person, Phone	None	Usual care
Riblet, 2022[364]	IG1	13	Other	2.5	Phone, Print, Video	None	Usual specialty MH care
Simon, 2022[365]	IG1	52	Case management	NR	Phone, Email or Text	None	Usual care
Simon, 2022[365]	IG2	52	DBT	NR	Phone, Web, Email or Text	None	Usual care
Torok, 2022[366]	IG1	6	DBT	0.6	Smartphone/App	None	Attention Control
Van Orden, 2021[359]	IG1	10	Social-behavioral activation	10	In-person	None	Usual care
van Spijker, 2014[358]	IG1	6	CBT	21	Web	None	Usual care

Table 49. Intervention Characteristics of Suicide Prevention Studies (KQ4)

Author, Year	IG	Duration, wks	Therapeutic Approach	Est Contact Hours	Delivery	PC Team Role	Control
Ward-Ciesielski, 2017[361]	IG1	0.14	DBT	0.8	In-person	None	Minimal

Abbreviations: CAMS = collaborative assessment and management of suicidality; CBT = cognitive behavioral therapy; DBT = dialectical behavior therapy; Est = estimated; IG = intervention group; IG1 = intervention group 1; MH = mental health; NR = not reported; PC = primary care.

Table 50. Summary of Evidence

Key Question Condition	No. of studies (N randomized)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Depression KQ1 (screening benefits)	14 RCTs, 3 CCTs (n=18,437)	Evidence supported the benefits of screening for depression. For example, ORs (95% CI) at 6 months post-baseline or 6 months postpartum (or the closest followup timepoint to 6 months) include: • Prevalence of depression or clinically important symptomatology: 0.60 ([0.50 to 0.73]; 8 studies [n=10,244]; I^2=0%) • Remission or falling below a specific level of depression symptomatology: 1.58 ([1.23 to 2.02]; 8 studies [n=2,302]; I^2=0%) However, no clear benefit in symptom severity measures was found (pooled MD in change, -1.0 [-2.3 to 0.3]; 9 studies [n=5,543], I^2=74.4%)	Reasonably consistent, reasonably precise	Few studies with unscreened control groups and limited capacity for conducting such studies, as screening for depression becomes the standard of care; heterogeneity in interventions and limited evidence on screening without further practice supports	Moderate for benefit	Most studies either conducted outside the US or, among US-based studies, published >15 years ago. Applicability to current US healthcare systems unclear.
Depression KQ2 (accuracy of screening tools)	10 ESRs (~196 studies, N~75,000), 14 test accuracy studies (N=8,819)	Adequate sensitivity and specificity for the PHQ-9 Linear, PHQ-8, PHQ-2, Whooley, CES-D, EPDS, and GDS.	Consistent, precise	Most of the ESRs were not restricted to primary care populations	High	Most of the studies were not conducted in the US.

Table 50. Summary of Evidence

Key Question Condition	No. of studies (N randomized)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Depression KQ3 (harms of screening)	Directly assessed harms: 1 (n=642) Indirectly used to infer harms: 14 RCTs, 3 CCTs (n=18,437)	One study reported no adverse events in either group. Studies included for KQ1 did not show a pattern of results indicating harmful impact.	Consistent, imprecise	Adverse events rarely directly assessed	Moderate for little to no harm	Most studies either conducted outside the US or, among US-based studies, published >15 years ago. Applicability to current US healthcare systems unclear.
Depression KQ4 (benefits of treatment)	30 ESRs of psychological treatment (≥346 RCTs, N~45,078) 10 ESRs of pharmacol-ogic treatment (≥522 studies, N ≥116,477)	Psychological treatment improved depression and other health outcomes such as anxiety symptoms, hopelessness, quality of life, and functioning. The broadest analysis indicated a moderate to large effect on depression (SMD, -0.72 [95% CI, -0.78 to -0.67]; k=385, N not reported, but estimated at approximately 33,000). The effect was smaller when limited to studies in primary care patients, but clearly statistically significant (SMD, -0.42 [95% CI, -0.56 to -0.29]; k=59, N not reported). Antidepressant medications consistently demonstrated increased rates of remission and response to treatment, and small but statistically significant reductions in depressive symptom severity. For example, fluoxetine, which had the largest body of evidence with 117 studies, was associated with a small reduction in symptom severity (SMD, -0.23 [95% CI, -0.28 to -0.19]), a 46% increase in the odds of remission (OR, 1.46 [95% CI, 1.34 to 1.60]) and a 52%	Consistent, precise	Most ESRs examined post-treatment outcomes with little information on longer-term followup. There was evidence of publication/ reporting bias, however effects were still statistically significant after adjusting for these biases. Evidence for benefit in a priori populations of interest was very limited in	High for benefit	Studies recruited from a wide range of community, online, and clinic sources, wide range of countries, and effect sizes in subgroup analyses limited to primary care settings tended to be smaller than broad-based analyses.

Table 50. Summary of Evidence

Key Question Condition	No. of studies (N randomized)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
		increase in the odds treatment response (OR, 1.52 [95% CI, 1.40 to 1.66], number of studies and individuals included in each specific analysis was not reported, nor were I^2 values) .		the synthesized literature, particularly on the effect of antidepressant medications.		
Depression KQ5 (harms of treatment)	4 ESRs of psychological treatment (~63 RCTs, N~8,466) 22 ESRs of pharmacol-ogic treatment k~697 studies, N >9 million 1 cohort study of pharmacol-ogic (N=358,351)	In 3 ESRs, deterioration rates were either lower with psychological interventions or did not differ statistically from control groups. A separate review among older adults reported that none of the 14 included trials reported safety data. Pharmacologic treatment was associated with a higher risk of dropout due of adverse events with all agents examined and a higher risk of serious adverse events with SSRI use (OR, 1.39 [95% CI 1.12 to 1.72], 44 RCTs, N not reported, I^2=0%). There were too few suicide deaths to determine the association between antidepressant use and suicide death, but both RCT and observational evidence supported an increased risk of suicide attempts with second generation antidepressant use among adults up to age 65 (OR, 1.53 [95% CI, 1.09 to 2.15]; N=41,861; 0.7% of antidepressants vs. 0.3% of placebo users). Other outcomes were largely limited to observational evidence.	Dropout due to adverse effects: Consistent, reasonably precise Suicide attempt: Consistent, Imprecise Other serious harms: Inconsistent, imprecise	Psychological: Harms not directly reported Pharmacologic: RCTs underpowered to identify rare serious outcomes, observational studies could not control for important confounders	Psychological: Low for little to no harm Pharmacol-ogic: Moderate for increased risk of non-serious harms Low for increased risk of serious harm	Population and settings characteristics were not reported in the ESRs.

Table 50. Summary of Evidence

Key Question Condition	No. of studies (N randomized)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Anxiety KQ1 (screening benefits)	2 RCTs (n=918)	Both studies found no group differences in anxiety or general mental health symptom severity at 13 to 22 weeks of followup. Absolute differences in change ranged from -1.5 to 0.3 on 16- and 40-point scales.	Reasonably consistent, Imprecise	Limited number of studies	Insufficient	Both conducted in US primary care settings, one study published in 1994 so may not reflect current practice.
Anxiety KQ2 (accuracy of screening tools)	10 test accuracy studies (n=6,463)	Adequate sensitivity and specificity for the GAD-7 to detect GAD. More limited evidence for the GAD-2 to detect GAD. GAD-7 and GAD-2 were less accurate for identifying any anxiety disorder. Limited evidence for the GAD-7, GAD-2, and PHQ-PD to detect PD. Limited evidence for the GAD-7 and GAD-2 to detect SAnD.	Reasonably consistent, reasonably precise	Few studies, limited replication	Moderate for the GAD-2/7 to detect GAD Low for all other instruments and conditions	Many studies were conducted in the US, but those limited to older adults and pregnant women and the largest general adult study were conducted outside of the US.
Anxiety KQ3 (harms of screening)	Directly assessed harms: 0 Indirectly used to infer harms: 2 RCTs (n=918)	No studies reported on harms of screening for anxiety. Studies included for KQ1 did not show a pattern of results indicating harmful impact.	Consistent, imprecise	Minimal evidence	Insufficient	Both studies included for KQ1 outcomes conducted in US primary care settings, one study published in 1994 so may not reflect current practice.
Anxiety KQ4 (benefits of treatment)	Psychological: 24 RCTs (N=5,307), 8 ESRs (~144 RCTs, N~11,030)	Psychological interventions showed a relatively small but statistically significant reduction in anxiety symptom severity in primary care patients with anxiety (SMD, -0.41 [95% CI, -0.58 to -0.23]; 10 RCTs [n=2,075]; I^2=40.2%), but not among mixed populations of people with anxiety or depression (SMD, -0.18 [95% CI, -0.39	Consistent, reasonably precise	Only 10 studies were among anxiety patients, others were in mixed populations with anxiety or depression;	High for benefit	24 studies in primary care populations, but only 7 conducted in the US; all studies reporting race or ethnicity included majority (57% to 82%) White participants.

Table 50. Summary of Evidence

Key Question Condition	No. of studies (N randomized)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
	Pharmacologic: 2 RCTs (N=423), 10 ESRs (~227 RCTs, N~40,803)	to 0.03]; 12 RCTs [n=1,868]; I^2=66.7%). In the ESRs (not limited to primary care patients), psychological treatment was associated with reduced anxiety symptoms; SMDs at post treatment among broad adult populations were -0.80 and larger and CBT was also associated with improved depression symptom severity and quality of life. More limited evidence suggested a benefit in older and perinatal patients as well. For pharmacologic treatment, 2 RCTs of venlafaxine and escitalopram in primary care patients both showed a benefit with antidepressant use. ESRs, not limited to primary care patients, reported improved anxiety and other outcomes for people taking antidepressants and benzodiazepines compared to placebo. For example, among patients with generalized anxiety disorder, the SMD for change in anxiety symptom severity with SSRIs was -0.66 (95% CI, -0.90 to -0.43, 31 studies, N and I^2 not reported).		limited evidence in older adults, limited evidence in perinatal patients; little information on outcomes beyond 8-12 weeks. There was evidence of publication and reporting bias among pharmacotherapy trials, however statistical significance remained after adjustment.		
Anxiety KQ5 (harms of treatment)	Psychological: 0 directly reported Inferred from KQ4 studies Pharmacologic: 3 RCTs (N=669), 8 ESRs (~112 RCTs,	None of the RCTs or ESRs of psychological treatment reported on adverse events, but there was no pattern of effects indicating an elevated risk of harm. For pharmacologic treatment, evidence indicated an increase in non-serious harms as measured by a higher percent of participants taking medication (vs. placebo) experiencing any adverse	Psychological: Consistent, imprecise Pharmacologic, non-serious: Consistent, reasonably precise	Specific serious outcomes were rare and studies were underpowered to identify; little information on outcomes beyond 8-12 weeks. Case-	Low for psychological for little to no harm Moderate for non-serious harms of pharmacotherapy	Population and settings characteristics were not reported in the ESRs.

Table 50. Summary of Evidence

Key Question Condition	No. of studies (N randomized)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
	N~29,674), 2 case-control (N=262,3780)	events and withdrawals due to adverse events. Serious adverse events were rare; case-control studies suggested a possible increased risk in suicide deaths and spontaneous abortion with benzodiazepine, but these data had important limitations.	Pharmacol-ogic, serious: Consistent, imprecise	control studies could not fully control for important confounders and study on suicide used only prescription as an exposure (rather than dispensings)	Insufficient for serious harms of pharmaco-therapy	
Suicide risk KQ1 (screening benefits)	1 RCT (n=443)	Among primary care patients who screened positive for depression, there was 1 suicide attempt after 2 weeks; there were no group differences on any of 3 items measuring suicidal ideation.	Consistency NA, imprecise	Single study, very short-term followup, limited to people who screened positive for depression	Insufficient	Conducted in the UK and limited to people with symptoms of depression.
Suicide risk KQ2 (accuracy of screening tools)	3 test accuracy studies (n=1,751)	GDS-15, GDS-SI, and the SDDS-PC had adequate test accuracy to detect suicidal ideation.	Consistency NA, precision, NA	Not replicated in more than 1 study.	Insufficient	All studies took place in the US, 2 in primary care.
Suicide risk KQ3 (harms of screening)	1 RCT (n=443)	Two of three suicidal ideation items indicated a possible higher risk with screening; however, the findings were inconclusive due to the lack of statistical significance and very wide confidence intervals.	Consistency NA, imprecise	Single study, very short-term followup, limited to people who screened positive for depression	Insufficient	Conducted in the UK and limited to people with symptoms of depression.

Table 50. Summary of Evidence

Key Question Condition	No. of studies (N randomized)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Suicide risk KQ4 (benefits of treatment)	23 RCTs (n=22,632)	A very large (n=18,882) study conducted in 4 US healthcare systems found that two separate suicide prevention interventions were associated with either no impact on suicide attempts (HR, 1.07 [97.5% CI, 0.84 to 1.37] for a care management intervention) or an *increased* risk of suicide attempts (HR, 1.29 [97.5% CI, 1.02 to 1.64] for a low-intensity online intervention). Most other studies had very few participants with suicide attempts and the pooled effect was not statistically significant (OR, 0.94 [95% CI, 0.73 to 1.22]; 12 RCTs [n=14,573]; I^2=11.2%). The impact of psychological interventions (e.g., dialectical and cognitive behavioral therapy) on suicide deaths could not be determined due to the small number of events. Although there was a small statistically significant benefit for depression symptom severity, there was no clear improvement over usual care for suicidal ideation, self-harm, other mental outcomes, or emergency or inpatient healthcare utilization. No studies tested a pharmacologic intervention compared with a placebo control.	Inconsistent, imprecise	Control groups were typically usual specialty mental health care (enhanced or optimized in some cases) so may be considered comparative effectiveness studies; some trials had primary aims of broad self-harm reduction (i.e., not focused on self-harm with suicidal intent)	Suicide death: Insufficient Suicide attempts: Moderate that some interventions are associated with no benefit or increased risk of harm compared with usual mental health care Suicide ideation, depression, other mental health: Low for small to no benefit compared with usual specialty mental health care	15 trials conducted in the US; primarily-White non-Hispanic participants; studies were required to have identified participants through outpatient or community settings, rather than through emergency or inpatient settings.

Table 50. Summary of Evidence

Key Question Condition	No. of studies (N randomized)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
Suicide risk KQ5 (harms of treatment)	Directly assessed harms: 2 (n=607) Indirectly used to infer harms: 15 RCTs (n=1,994)	Two studies reported on harms. There were no differences between groups at followup on an instrument designed to assess the perceived level of coercion experienced by service users during hospital admission. The study of lithium found a higher rate of non-serious adverse events (75.7% with lithium, 69% with placebo, p-value not reported), a slightly higher rates of serious adverse events (38.8% with lithium, 34.1% with placebo, p-value not reported) but no difference in withdrawals due to adverse events (1.2% with lithium, 1.5% with placebo, p-value not reported). There was no pattern of effect in the studies included for KQ4 to indicate paradoxical harms of treatment.	Consistent, imprecise	Minimal evidence	Low	15 trials conducted in the US; primarily-White non-Hispanic participants; studies were required to have identified participants through outpatient or community settings, rather than through emergency or inpatient settings.

Abbreviations: CBT = cognitive behavioral therapy; CCTs = controlled clinical trials; CES-D = Center for Epidemiologic Studies Depression Scale; CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale; ESRs = existing systematic reviews; GAD = generalized anxiety disorder; GAD-2 = Generalized Anxiety Disorder 2-Item Scale; GAD-7 = Generalized Anxiety Disorder 7-Item Scale; GDS = Geriatric Depression Scale; HR = hazard ratio; k = number of trials; KQ = key question; MD = mean difference; N = number of participants; NA = not applicable; OR = odds ratio; PD = panic disorder; PHQ = Patient Health Questionnaire; PHQ-PD = Patient Health Questionnaire-Panic Disorder; RCTs = randomized controlled trials; SAnD = social anxiety disorder; SDDS-PC = Symptom Driven Diagnostic System for Primary Care; SMD = standardized mean difference; SSRIs = selective serotonin reuptake inhibitors; UK = United Kingdom; US = United States

Search Strategy

Original search – Date delivered: 6/12/20
Bridge 1 – Date delivered: 9/24/21
Bridge 2 – Date delivered: 9/7/22

Screening, psychotherapy, and pharmacotherapy trials

Sources Searched: database and platform
MEDLINE via Ovid
Cochrane Central Register of Controlled Clinical Trials via Wiley
PsycInfo via Ovid

Screening instruments

Sources Searched: database and platform
MEDLINE via Ovid
Cochrane Central Register of Controlled Clinical Trials via Wiley
PsycInfo via Ovid

Key:
/ = MeSH subject heading
$ = truncation
ti = word in title
ab = word in abstract
pt = publication type
* = truncation
kw = keyword
adj = adjacent
md = methods
po = population

Medline

Medline Screening, psychotherapy and pharmacotherapy trials bridge search 2:

Ovid MEDLINE(R) ALL <1946 to September 06, 2022>

1	Depression/	143555
2	Depressive Disorder/	74755
3	Depressive Disorder, Major/	36338
4	Dysthymic Disorder/	1171
5	depressive disorder, treatment-resistant/	1972
6	Depression, Postpartum/	6992
7	(depress$ or dysthym$).ti.	173632
8	(depress$ adj3 disorder$).ti,ab.	65779
9	(depress$ or dysthym$).ti,ab.	529334
10	limit 9 to ("in data review" or in process or publisher or "pubmed not medline")	62055
11	or/1-8,10	345293
12	limit 11 to (english language and yr="2014 -Current")	148910
13	anxiety disorders/	39511

14 panic disorder/ 7225
15 phobic disorders/ 11124
16 Phobia, Social/ 1103
17 (anxiet$ or overanxious or anxious$ or phobia$ or phobic or panic).ti. 75260
18 ((anxiet$ or overanxious or anxious$ or phobia$ or phobic or panic) adj3 disorder$).ti,ab. 52620
19 or/13-18 120836
20 limit 19 to (english language and yr="1990 -Current") 99331
21 suicide/43725
22 suicidal ideation/ 11272
23 suicide, attempted/ 22198
24 Suicide, Completed/ 267
25 Self-Injurious Behavior/ 9385
26 (suicid$ or parasuicid$ or self harm$ or Self Injur$).ti. 55339
27 or/21-26 82736
28 limit 27 to (english language and yr="2012 -Current") 33920
29 12 or 20 or 28 251944
30 Mass screening/ 114430
31 (screen$ or casefinding or case finding or "trained to identify" or "trained in identifying").ti,ab. or (diagnos$ or detect$ or identif$).ti. 2196135
32 30 or 31 2221747
33 (clinical trial or adaptive clinical trial or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or equivalence trial or pragmatic clinical trial or Meta-Analysis).pt. 1091511
34 clinical trials as topic/ or adaptive clinical trials as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or non-randomized controlled trials as topic/ or randomized controlled trials as topic/ or equivalence trials as topic/ or intention to treat analysis/ or pragmatic clinical trials as topic/ or meta-analysis as topic/ 383613
35 control groups/ or double-blind method/ or single-blind method/ or random allocation/ or placebos/ 323068
36 (randomized or randomised or placebo or randomly or phase iii or phase 3).ti,ab. 1162933
37 (RCT or sham or dummy or single blind$ or double blind$ or allocated or allocation or triple blind$ or treble blind$).ti,ab. 427756
38 ((control$ or clinical) adj3 (study or studies or trial$ or group$)).ti,ab. 1769266
39 (Nonrandom$ or non random$ or non-random$ or quasi-random$ or quasirandom$).ti,ab. 50919
40 ((open label or open-label) adj5 (study or studies or trial$)).ti,ab. 42031
41 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial$)).ti,ab. 10434
42 (pragmatic study or pragmatic studies).ti,ab. 533
43 ((pragmatic or practical) adj3 trial$).ti,ab. 5285
44 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial$ or design)).ti,ab. 15227
45 (metaanaly$ or meta analy$).ti,ab. 245180
46 or/33-45 3159250
47 29 and 32 and 46 5479
48 remove duplicates from 47 5446

49 limit 19 to (english language and yr="2015 -Current") 48642
50 limit 27 to (english language and yr="2012 -Current") 33920
51 49 or 50 81404
52 46 and 51 16250
53 exp Psychotherapy/ 213730
54 Counseling/ 38907
55 Directive Counseling/ 2429
56 Problem Solving/ 26484
57 psychoanalysis/ 9853
58 motivational interviewing/ 2437
59 psychotherap$.ti,ab. 46623
60 (psychological adj5 (therap$ or treatment$ or intervention$)).ti,ab. 27190
61 (psychosocial adj5 (therap$ or treatment$ or intervention$)).ti,ab. 15790
62 (behavi$ adj5 (therap$ or treatment$ or intervention$)).ti,ab. 93177
63 (cognitive adj5 (therap$ or treatment$ or intervention$)).ti,ab. 50022
64 (psychodynamic adj5 (therap$ or treatment$ or intervention$)).ti,ab. 1775
65 (nondirective adj5 (therap$ or treatment$ or intervention$)).ti,ab. 126
66 (non directive adj5 (therap$ or treatment$ or intervention$)).ti,ab. 100
67 interpersonal therap$.ti,ab. 421
68 interpersonal psychotherap$.ti,ab. 977
69 interpersonal intervention$.ti,ab. 51
70 supportive therap$.ti,ab. 5261
71 group therap$.ti,ab. 5145
72 counsel$.ti,ab. 126423
73 psychoeducat$.ti,ab. 6423
74 (problem solving treatment or problem solving therapy).ti,ab. 621
75 motivational interview$.ti,ab. 4975
76 psychoanal$.ti,ab. 14387
77 family therapy.ti,ab. 3413
78 ((limit or limits or limiting or limited or restrict$ or barrier$) adj3 (access$ or mean$ or method or methods or availab$ or suicid$)).ti,ab. 102632
79 ((limit or limits or limiting or limited or restrict$ or barrier$ or safety) and (prevent$ or jumping or hanging or charcoal burning or poisoning or drowning or pesticide$ or firearm$ or gunshot or overdose$)).ti,ab. 273376
80 (Postcard or letter or telephone or writing or educational intervention or visited or home visit or outreach program$).ti,ab. 238110
81 27 and (78 or 79 or 80) 4218
82 cbt.ti,ab. 13189
83 limit 82 to ("in data review" or in process or publisher or "pubmed not medline") 2164
84 or/53-77,81,83 511835
85 52 and 84 5245
86 remove duplicates from 85 5221
87 Antidepressive Agents/ or Antidepressive Agents, Second-Generation/ 54293
88 (anti-depress$ or antidepress$ or pharmacotherap$).ti,ab. 113418
89 Serotonin Uptake Inhibitors/ 20763
90 (serotonin reuptake or serotonin re-uptake or serotonin uptake or ssri$).ti,ab. 21258
91 (serotonergic adj (drug$ or agent$ or medicat$)).ti,ab. 1294
92 Citalopram/ or (citalopram or celexa or escitalopram or Lexapro).ti,ab. 8466

93 Fluoxetine/ or (fluoxetine or fluoxetin or Prozac).ti,ab. 15196
94 fluvoxamine/ or fluvoxamin$.ti,ab. 3193
95 Paroxetine/ or (paroxetine or paxil or seroxat).ti,ab. 6685
96 Sertraline/ or (sertraline or Zoloft).ti,ab. 5744
97 "Serotonin and Noradrenaline Reuptake Inhibitors"/ 481
98 (serotonin norepinephrine reuptake inhibitor$ or "selective serotonin and noradrenaline reuptake inhibitor$" or serotonin noradrenaline uptake inhibitor$ or "selective serotonin and noradrenaline uptake inhibitor$" or SNRI$ or SSNRI$).ti,ab. 2329
99 Duloxetine Hydrochloride/ or (duloxetine or Cymbalta).ti,ab. 3075
100 Desvenlafaxine Succinate/ or desvenlafaxine.ti,ab. 503
101 milnacipran/ or levomilnacipran/ or (milnacipran or levomilnacipran or Fetzima).ti,ab. 796
102 Venlafaxine Hydrochloride/ or (venlafaxine or Effexor).ti,ab. 4798
103 (serotonin modulator or serotonin stimulator).ti,ab. 13
104 (Nefazodone or serzone or dutonin or nefadar or CYP3A4).ti,ab. 11247
105 trazodone/ or (Trazodon$ or desyrel).ti,ab. 2263
106 vilazodone hydrochloride/ or Vilazodone.ti,ab. 243
107 vortioxetine/ or Vortioxetine.ti,ab. 577
108 Bupropion/ or (bupropion or Wellbutrin or amfebutamone or zyban).ti,ab. 5374
109 Mirtazapine/ or (mirtazapine or esmirtazapine or Remeron).ti,ab. 2611
110 Antidepressive Agents, Tricyclic/ 10520
111 Imipramine/ or (imipramine or Tofranil).ti,ab. 13440
112 amitriptyline/ or (amitriptyline or Elavil).ti,ab. 9717
113 nortriptyline/ or (nortriptyline or Pamelor or Aventyl).ti,ab. 3217
114 protriptyline/ or (protriptyline or Vivactil).ti,ab. 416
115 clomipramine/ or (clomipramine or Anafranil).ti,ab. 4120
116 desipramine/ or (desipramine or Norpramin).ti,ab. 7934
117 trimipramine/ or (trimipramine or Surmontil).ti,ab. 550
118 Doxepin/ or (doxepin or Sinequan).ti,ab.1500
119 Amoxapine/ or amoxapine.ti,ab. 478
120 Maprotiline/ or (Maprotiline or Ludiomil).ti,ab. 1325
121 Buspirone/ or (buspirone or buspar).ti,ab. 3071
122 Pregnanolone/ or (brexanolone or Allopregnanolone or Zulresso).ti,ab. 2570
123 Lithium/ or exp Lithium Compounds/ or Lithium$.ti,ab. 66681
124 Anti-anxiety agents/ 19342
125 (Anti-anxiet$ or antianxiety$ or anxiolytic or anti-panic or antipanic).ti,ab. 15790
126 benzodiazepines/ or benzodiazepinones/ or benzodiazepin$.ti,ab. 50954
127 alprazolam/ or (Alprazolam or Xanax).ti,ab. 2858
128 bromazepam/ or (bromazepam or lexotan or lexotanil).ti,ab. 617
129 chlordiazepoxide/ or (Chlordiazepoxide or Librium or Chlozepid or Elenium).ti,ab. 4839
130 clobazam/ or (Clobazam or Onfi or Frisium).ti,ab. 1146
131 clonazepam/ or (Clonazepam or Antelepsin or Rivotril).ti,ab. 4823
132 clorazepate dipotassium/ or (Clorazepate or Chlorazepate or Tranxene or Tranxilium or Tranex or Belseren or 4306-CB or 4306CB).ti,ab. 551
133 diazepam/ or (Diazepam or Valium or Faustan or Seduxen or Sibazon or Stesolid or Apaurin).ti,ab. 26433
134 estazolam/ or (Estazolam or Tasedan or D-40TA or D40TA).ti,ab. 286
135 flurazepam/ or (Flurazepam or Dalmane or Dalmadorm).ti,ab. 1190
136 (Halazepam or paxipam or Alapryl or Pacinone).ti,ab. 56

137 lorazepam/ or (Lorazepam or Ativan or Sinestron or WY-4036 or WY4036).ti,ab. 5006
138 oxazepam/ or (Oxazepam or Serax or Tazepam or Adumbran).ti,ab. 2019
139 temazepam/ or (temazepam or Restoril or Norkotral).ti,ab. 1146
140 or/87-139 338222
141 52 and 140 1897
142 remove duplicates from 141 1893
143 48 or 86 or 142 11486
144 143 not ((exp infant/ or child/ or adolescence/) not (exp adult/ or exp aged/ or middle aged/)) 10273
145 144 not (animals/ not humans/) 9992
146 (202109* or 202110* or 202111* or 202112* or 2022*).dt,da,ez. 2113883
147 145 and 146 2064

Screening instruments

Medline screening instruments bridge search 2:

Ovid MEDLINE(R) ALL <1946 to September 06, 2022>

1 Depression/ 143555
2 Depressive Disorder/ 74755
3 Depressive Disorder, Major/ 36338
4 Dysthymic Disorder/ 1171
5 depressive disorder, treatment-resistant/ 1972
6 Depression, Postpartum/ 6992
7 (depress$ or dysthym$).ti. 173632
8 (depress$ adj3 disorder$).ti,ab. 65779
9 (depress$ or dysthym$).ti,ab. 529334
10 limit 9 to ("in data review" or in process or publisher or "pubmed not medline") 62055
11 or/1-8,10 345293
12 limit 11 to (english language and yr="2014 -Current") 148910
13 anxiety disorders/ 39511
14 panic disorder/ 7225
15 phobic disorders/ 11124
16 Phobia, Social/ 1103
17 (anxiet$ or overanxious or anxious$ or phobia$ or phobic or panic).ti. 75260
18 ((anxiet$ or overanxious or anxious$ or phobia$ or phobic or panic) adj3 disorder$).ti,ab. 52620
19 or/13-18 120836
20 limit 19 to (english language and yr="2014 -Current") 53086
21 suicide/43725
22 suicidal ideation/ 11272
23 suicide, attempted/ 22198
24 Suicide, Completed/ 267
25 Self-Injurious Behavior/ 9385
26 (suicid$ or parasuicid$ or self harm$ or Self Injur$).ti. 55339
27 or/21-26 82736
28 limit 27 to (english language and yr="2012 -Current") 33920
29 12 or 20 or 28 205922
30 *Mass Screening/is, mt [Instrumentation, Methods] 20438

31 *"Surveys and Questionnaires"/ 49921
32 *Interview/ 0
33 *Psychiatric Status Rating Scales/ 11043
34 *Self Report/ 7566
35 screen$.ti. 203799
36 casefinding.ti,ab. 88
37 case finding.ti,ab. 5567
38 self report$.ti. 21338
39 (suicid$ adj3 (scale$ or inventor$ or questionnaire$ or survey$ or index$ or checklist$ or interview$ or screen$ or self report)).ti,ab. 4367
40 ((depress$ or anxiety) adj3 (scale$ or inventor$ or questionnaire$ or survey$ or index$ or checklist$ or interview$ or screen$ or self report)).ti. 6967
41 limit 40 to ("in data review" or in process or publisher or "pubmed not medline") 847
42 Patient Health Questionnaire/ 865
43 Patient Health Questionnaire.ti,ab. 8756
44 (PHQ-2 or PHQ-9 or PHQ-ADS).ti,ab. 5970
45 Primary Care Evaluation of Mental Disorders.ti,ab. 254
46 PRIME-MD.ti,ab. 329
47 (Center and Epidemiologic and Depression and Scale).ti,ab. 3885
48 (CES-D or CESD$).ti,ab. 5160
49 ("Edinburgh Postpartum Depression Scale" or "Edinburgh Postnatal Depression Scale").ti,ab. 3242
50 EPDS.ti,ab. 2468
51 (Geriatric Depression adj2 Scale$).ti,ab. 4532
52 GDS-15.ti,ab. 629
53 Generali?ed Anxiety Disorder Scale.ti,ab. 617
54 (GAD-2 or GAD-7).ti,ab. 2630
55 Geriatric Anxiety Inventory.ti,ab. 103
56 GAI-SF.ti,ab. 17
57 Geriatric Anxiety Scale.ti,ab. 36
58 (GAS-LTC or GAS-10).ti,ab. 60
59 ((Harkavy$ or Asnis$) and suicid$).ti,ab. 3
60 suicide probability.ti,ab.104
61 suicide status form.ti,ab. 18
62 (paykel$ and suicid$).ti,ab. 49
63 (self harm adj3 questionnaire$).ti,ab. 66
64 (self harm adj3 scale$).ti,ab. 53
65 (self harm adj3 survey$).ti,ab. 20
66 (self harm adj3 inventory).ti,ab. 116
67 (manchester and self harm).ti,ab. 54
68 suicide assessment.ti,ab. 245
69 (beck depression and suicid$).ti,ab. 801
70 (hamilton rating and suicid$).ti,ab. 199
71 (symptom driven diagnos$ and suicid$).ti,ab. 4
72 or/30-39,41-71 324077
73 "Sensitivity and Specificity"/ 365816
74 "Predictive Value of Tests"/ 221405
75 ROC Curve/ 69467

76 Receiver operat$.ti,ab. 114465
77 ROC curve$.ti,ab. 48646
78 sensitivit$.ti,ab. 945331
79 specificit$.ti,ab. 555143
80 (predictive value or "can be detected").ti,ab. 142885
81 accuracy.ti,ab. 501574
82 False Negative Reactions/ 18295
83 False Positive Reactions/ 28576
84 Diagnostic Errors/ 39422
85 "Reproducibility of Results"/ 449213
86 Reference Values/ 163523
87 Reference Standards/ 45425
88 Observer Variation/ 44726
89 Psychometrics/ 85781
90 Psychometric$.ti,ab. 56362
91 false positive$.ti,ab. 65800
92 false negative$.ti,ab. 37195
93 miss rate$.ti,ab. 623
94 error rate$.ti,ab. 16961
95 or/73-94 2635868
96 29 and 72 and 95 4669
97 29 and 72 23139
98 limit 97 to (systematic reviews pre 2019 or systematic reviews) 680
99 96 or 98 5087
100 99 not ((exp infant/ or child/ or adolescence/) not (exp adult/ or exp aged/ or middle aged/)) 4654
101 (202109* or 202110* or 202111* or 202112* or 2022*).dt,da,ez. 2113883
102 100 and 101 778

Cochrane Central Register of Controlled Clinical Trials (CENTRAL)

SADS screening and therapy

Cochrane screening and therapy bridge 2:

Date Run: 07/09/2022 21:03:46

ID Search Hits

#1 (depress* or dysthym*):ti or (depress* near/3 disorder*):ti,ab with Publication Year from 2014 to present, in Trials 17204

#2 (anxiet* or overanxious or anxious* or phobia* or phobic or panic):ti or ((anxiet* or overanxious or anxious* or phobia* or phobic or panic) near/3 (disorder*)):ti,ab with Publication Year from 1990 to present, in Trials 20865

#3 (suicid* or parasuicid* or self NEXT harm* or Self NEXT Injur*):ti,ab with Publication Year from 2012 to present, in Trials 5006

#4 #1 or #2 or #3 38134

#5 (screen* or casefinding or "case finding" or "trained to identify" or "trained in identifying"):ti,ab or (diagnos* or detect* or identif*):ti 111737

#6 #4 and #5 3775

#7 (anxiet* or overanxious or anxious* or phobia* or phobic or panic):ti or ((anxiet* or overanxious or anxious* or phobia* or phobic or panic) near/3 (disorder*)):ti,ab with Publication Year from 2015 to present, in Trials 11103
#8 (suicid* or parasuicid* or self NEXT harm* or Self NEXT Injur*):ti,ab with Publication Year from 2012 to present, in Trials 5006
#9 #7 or #8 15744
#10 psychotherap*:ti,ab 8591
#11 ((psychological or psychosocial or behavi* or cognitive or psychodynamic or nondirective) near/5 (therap* or treatment* or intervention*)):ti,ab 61677
#12 (non directive near/5 (therap* or treatment* or intervention*)):ti,ab 85
#13 interpersonal NEXT therap*:ti,ab 190
#14 interpersonal NEXT psychotherap*:ti,ab 673
#15 interpersonal NEXT intervention*:ti,ab 6
#16 supportive NEXT therap*:ti,ab 1015
#17 group NEXT therap*:ti,ab 2530
#18 counsel*:ti,ab 23574
#19 psychoeducat*:ti,ab 5184
#20 ("problem solving treatment" or "problem solving therapy"):ti,ab 635
#21 Motivational NEXT interview*:ti,ab 4261
#22 psychoanal*:ti,ab 234
#23 family NEXT therapy:ti,ab 559
#24 ((limit or limits or limiting or limited or restrict* or barrier*) near/3 (access* or mean* or method or methods or availab* or suicid*)):ti,ab 8306
#25 ((limit or limits or limiting or limited or restrict* or barrier* or safety) and (prevent* or jumping or hanging or "charcoal burning" or poisoning or drowning or pesticide* or firearm* or gunshot or overdose*)):ti,ab 38549
#26 (Postcard or letter or telephone or writing or "educational intervention" or visited or "home visit" or outreach NEAR program*):ti,ab 40554
#27 cbt:ti,ab 9693
#28 1-#27 165493
#29 #9 and #28 6184
#30 (anti-depress* or antidepress* or pharmacotherap*):ti,ab 20614
#31 ("serotonin reuptake" or "serotonin re-uptake" or "serotonin uptake" or ssri*):ti,ab 4722
#32 (serotonergic near/1 (drug* or agent* or medicat*)):ti,ab 175
#33 (citalopram or celexa or escitalopram or Lexapro or fluoxetine or fluoxetin or Prozac or fluvoxamin* or paroxetine or paxil or seroxat or sertraline or Zoloft):ti,ab 10640
#34 ("serotonin norepinephrine reuptake" or "selective serotonin and noradrenaline reuptake" or "serotonin noradrenaline uptake" or "selective serotonin and noradrenaline uptake" or SNRI* or SSNRI*):ti,ab 622
#35 (duloxetine OR Cymbalta or desvenlafaxine or milnacipran OR levomilnacipran OR Fetzima or venlafaxine OR Effexor or "serotonin modulator" or "serotonin stimulator" or Nefazodone or serzone or dutonin or nefadar or CYP3A4 or Trazodon* or desyrel or Vilazodone or Vortioxetine or bupropion OR Wellbutrin OR amfebutamone OR zyban or mirtazapine OR esmirtazapine OR Remeron):ti,ab 8013
#36 (imipramine or Tofranil or amitriptyline or Elavil or nortriptyline or Pamelor or Aventyl or protriptyline or Vivactil or clomipramine or Anafranil or desipramine or Norpramin or trimipramine or Surmontil or doxepin or Sinequan or amoxapine or Maprotiline or Ludiomil or buspirone or buspar or brexanolone or Allopregnanolone or Zulresso or Lithium*):ti,ab 9915
#37 (Anti-anxiet* or antianxiety* or anxiolytic or anti-panic or antipanic):ti,ab 2796

#38 (benzodiazepin* or Alprazolam or Xanax or bromazepam or lexotan or lexotanil or Chlordiazepoxide or Librium or Chlozepid or Elenium or Clobazam or Onfi or Frisium or Clonazepam or Antelepsin or Rivotril or Clorazepate or Chlorazepate or Tranxene or Tranxilium or Tranex or Belseren or Diazepam or Valium or Faustan or Seduxen or Sibazon or Stesolid or Apaurin or Estazolam or Tasedan or D-40TA or D40TA or Flurazepam or Dalmane or Dalmadorm or Halazepam or paxipam or Alapryl or Pacinone or Lorazepam or Ativan or Sinestron or WY-4036 or WY4036 or Oxazepam or Serax or Tazepam or Adumbran or temazepam or Restoril or Norkotral):ti,ab 10961
#39 2-#38 50914
#40 #9 and #39 2114
#41 #6 or #29 or #40 10206
#42 #41 NOT (pubmed):an with Cochrane Library publication date from Sep 2021 to present 1257

SADS screening instruments

Cochrane screening instruments original bridge 2:

Date Run: 07/09/2022 21:11:26
ID Search Hits
#1 (depress* or dysthym*):ti or (depress* near/3 disorder*):ti,ab with Publication Year from 2014 to present, in Trials 17204
#2 (anxiet* or overanxious or anxious* or phobia* or phobic or panic):ti or ((anxiet* or overanxious or anxious* or phobia* or phobic or panic) near/3 (disorder*)):ti,ab with Publication Year from 2014 to present, in Trials 12039
#3 (suicid* or parasuicid* or self NEXT harm* or Self NEXT Injur*):ti,ab with Publication Year from 2012 to present, in Trials 5006
#4 #1 or #2 or #3 29347
#5 (screen* or self NEXT report*):ti13054
#6 (casefinding or case NEXT finding):ti,ab 407
#7 (suicid* near/3 (scale* or inventor* or questionnaire* or survey* or index* or checklist* or interview* or screen* or self report)):ti,ab 1595
#8 ((depress* or anxiety) near/3 (scale* or inventor* or questionnaire* or survey* or index* or checklist* or interview* or screen* or self report)):ti 986
#9 ("Patient Health Questionnaire" or PHQ-2 OR PHQ-9 or PHQ-ADS):ti,ab 3620
#10 ("Primary Care Evaluation of Mental Disorders" or PRIME-MD):ti,ab 57
#11 (Center and Epidemiologic and Depression and Scale):ti,ab 657
#12 (CES-D or CESD*):ti,ab 1180
#13 ("Edinburgh Postpartum Depression Scale" or "Edinburgh Postnatal Depression Scale" or EPDS):ti,ab 920
#14 (Geriatric Depression near/2 Scale*):ti,ab 1493
#15 GDS-15:ti,ab 186
#16 Generali?ed NEXT "Anxiety Disorder Scale":ti,ab 181
#17 (GAD-2 or GAD-7):ti,ab 1316
#18 "Geriatric Anxiety Inventory":ti,ab 62
#19 GAI-SF:ti,ab 3
#20 "Geriatric Anxiety Scale":ti,ab 16
#21 (GAS-LTC or GAS-10):ti,ab 8
#22 (Harkavy* or Asnis*):ti,ab 192
#23 "suicide probability":ti,ab 6
#24 "suicide status form":ti,ab 3

#25 paykel*:ti,ab 247
#26 ("self harm" near/3 questionnaire*):ti,ab 12
#27 ("self harm" near/3 scale*):ti,ab 16
#28 ("self harm" near/3 survey*):ti,ab 1
#29 ("self harm" near/3 inventory):ti,ab 35
#30 (manchester and "self harm"):ti,ab 12
#31 "suicide assessment":ti,ab 41
#32 ("beck depression" and suicid*):ti,ab 273
#33 ("hamilton rating" and suicid*):ti,ab 142
#34 (("symptom driven" NEXT diagnos*) and suicid*):ti,ab 0
#35 3-#34 23796
#36 #4 and #35 5100
#37 #36 NOT (pubmed):an with Cochrane Library publication date from Sep 2021 to present 687

PsycInfo

Screening, psychotherapy, and pharmacotherapy trials original search

PsycInfo screening, psychotherapy, and pharmacotherapy trials bridge 2:

APA PsycInfo <1806 to August Week 5 2022>
1 exp major depression/ 150508
2 (depress$ or dysthym$).ti. or (depress$ adj3 disorder$).ti,ab. or dysthym$.ti,ab. 155080
3 1 or 2 195745
4 limit 3 to (english language and yr="2014 -Current") 68470
5 Anxiety Disorders/ or Generalized Anxiety Disorder/ or Panic Disorder/ or Social Anxiety/ 34650
6 (anxiet$ or overanxious or anxious$ or phobia$ or phobic or panic).ti. 75038
7 ((anxiet$ or overanxious or anxious$ or phobia$ or phobic or panic) adj3 disorder$).ti,ab. 52653
8 or/5-7 105293
9 limit 8 to (english language and yr="1990 -Current") 81444
10 Suicide/ or Attempted Suicide/ or Suicidality/ or Suicidal Ideation/ or exp Self-Injurious Behavior/ 49241
11 (suicid$ or parasuicid$ or self harm$ or Self Injur$).ti. 44620
12 10 or 11 54464
13 limit 12 to (english language and yr="2012 -Current") 22539
14 4 or 9 or 13 156401
15 screening/ 10014
16 (screen$ or casefinding or case finding or "trained to identify" or "trained in identifying").ti,ab. or (diagnos$ or detect$ or identif$).ti. 208017
17 15 or 16 208754
18 exp clinical trials/ 13333
19 clinical trial.md. 34531
20 Experiment Controls/ or Random Sampling/ or Placebo/ 8113
21 (randomized or randomised or placebo or randomly or phase iii or phase 3 or RCT or sham or dummy or single blind$ or double blind$ or allocated or allocation or triple blind$ or treble blind$ or Nonrandom$ or non random$ or non-random$ or quasi-random$ or quasirandom$ or pragmatic study or pragmatic studies or metaanaly$ or meta analy$).ti,ab. 270583
22 ((control$ or clinical) adj3 (study or studies or trial$ or group$)).ti,ab. 245364

23 ((open label or open-label) adj5 (study or studies or trial$)).ti,ab. 5015
24 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial$)).ti,ab. 1111
25 ((pragmatic or practical) adj3 trial$).ti,ab. 989
26 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial$ or design)).ti,ab. 10966
27 or/18-26 435297
28 14 and 17 and 27 2575
29 limit 8 to (english language and yr="2015 -Current") 29679
30 limit 12 to (english language and yr="2012 -Current") 22539
31 29 or 30 51529
32 27 and 31 9317
33 exp Psychotherapy/ or Counseling/ or Psychotherapeutic Counseling/ or Cognitive Therapy/ or Anxiety Management/ or Behavior Therapy/ 258989
34 (psychotherap$ or interpersonal therap$ or interpersonal psychotherap$ or interpersonal intervention$ or supportive therap$ or group therap$ or counsel$ or psychoeducat$ or problem solving treatment or problem solving therapy or motivational interview$ or psychoanal$ or family therapy).ti,ab. 317821
35 ((psychological or psychosocial or behavi$ or cognitive or psychodynamic or nondirective or non directive) adj5 (therap$ or treatment$ or intervention$)).ti,ab. 158735
36 cbt.ti. 1841
37 ((limit or limits or limiting or limited or restrict$ or barrier$) adj3 (access$ or mean$ or method or methods or availab$ or suicid$)).ti,ab. 20075
38 ((limit or limits or limiting or limited or restrict$ or barrier$ or safety) and (prevent$ or jumping or hanging or charcoal burning or poisoning or drowning or pesticide$ or firearm$ or gunshot or overdose$)).ti,ab. 41207
39 (Postcard or letter or telephone or writing or educational intervention or visited or home visit or outreach program$).ti,ab. 117163
40 12 and (37 or 38 or 39) 3509
41 or/33-36,40 520490
42 32 and 41 3178
43 Antidepressant Drugs/ or Serotonin Reuptake Inhibitors/ or Citalopram/ or Fluoxetine/ or Fluvoxamine/ or Paroxetine/ or Serotonin Norepinephrine Reuptake Inhibitors/ or Venlafaxine/ or Trazodone/ or Bupropion/ or Tricyclic Antidepressant Drugs/ or Imipramine/ or Amitriptyline/ or Nortriptyline/ or Chlorimipramine/ or Desipramine/ or Doxepin/ or Maprotiline/ or Buspirone/ or Lithium/ or Lithium Carbonate/ or Minor Tranquilizers/ or Alprazolam/ or Chlordiazepoxide/ or Clonazepam/ or Diazepam/ or Lorazepam/ or Oxazepam/ or Benzodiazepines/ or Flurazepam/ 52622
44 (anti-depress$ or antidepress$ or pharmacotherap$ or serotonin reuptake or serotonin re-uptake or serotonin uptake or ssri$ or citalopram or celexa or escitalopram or Lexapro or fluoxetine or fluoxetin or Prozac or fluvoxamin$ or paroxetine or paxil or seroxat or sertraline or Zoloft or serotonin norepinephrine reuptake inhibitor$ or "selective serotonin and noradrenaline reuptake inhibitor$" or serotonin noradrenaline uptake inhibitor$ or "selective serotonin and noradrenaline uptake inhibitor$" or SNRI$ or SSNRI$ or duloxetine or Cymbalta or desvenlafaxine or milnacipran or levomilnaipran or Fetzima or venlafaxine or Effexor or serotonin modulator or serotonin stimulator or Nefazodone or serzone or dutonin or nefadar or CYP3A4 or Trazodon$ or desyrel or Vilazodone or Vortioxetine or bupropion or Wellbutrin or amfebutamone or zyban or mirtazapine or esmirtazapine or Remeron or imipramine or Tofranil or amitriptyline or Elavil or nortriptyline or Pamelor or Aventyl or protriptyline or Vivactil or clomipramine or Anafranil or desipramine or Norpramin or trimipramine or Surmontil or

doxepin or Sinequan or amoxapine or Maprotiline or Ludiomil or buspirone or buspar or brexanolone or Allopregnanolone or Zulresso or Lithium$ or Anti-anxiet$ or antianxiety$ or anxiolytic or anti-panic or antipanic or benzodiazepin$ or Alprazolam or Xanax or bromazepam or lexotan or lexotanil or Chlordiazepoxide or Librium or Chlozepid or Elenium or Clobazam or Onfi or Frisium or Clonazepam or Antelepsin or Rivotril or Clorazepate or Chlorazepate or Tranxene or Tranxilium or Tranex or Belseren or 4306-CB or 4306CB or Diazepam or Valium or Faustan or Seduxen or Sibazon or Stesolid or Apaurin or Estazolam or Tasedan or D-40TA or D40TA or Flurazepam or Dalmane or Dalmadorm or Halazepam or paxipam or Alapryl or Pacinone or Lorazepam or Ativan or Sinestron or WY-4036 or WY4036 or Oxazepam or Serax or Tazepam or Adumbran or temazepam or Restoril or Norkotral).ti,ab. 102376
45 (serotonergic adj (drug$ or agent$ or medicat$)).ti,ab. 686
46 43 or 44 or 45 104848
47 32 and 46 999
48 28 or 42 or 47 6129
49 48 not (Animal not Human).po. 6015
50 limit 49 to (childhood <birth to 12 years> or adolescence <13 to 17 years>) 1215
51 limit 49 to adulthood <18+ years> 3762
52 50 not 51 661
53 49 not 52 5354
54 (202109* or 202110* or 202111* or 202112* or 2022*).ch. 155080
55 (202109* or 202110* or 202111* or 202112* or 2022*).up. 189520
56 54 or 55 320754
57 53 and 56 938

Screening instruments:

PsycInfo screening instruments bridge search 2:

APA PsycInfo <1806 to August Week 5 2022>
1 exp major depression/ 150508
2 (depress$ or dysthym$).ti. or (depress$ adj3 disorder$).ti,ab. or dysthym$.ti,ab. 155080
3 1 or 2 195745
4 limit 3 to (english language and yr="2014 -Current") 68470
5 Anxiety Disorders/ or Generalized Anxiety Disorder/ or Panic Disorder/ or Social Anxiety/ 34650
6 (anxiet$ or overanxious or anxious$ or phobia$ or phobic or panic).ti. 75038
7 ((anxiet$ or overanxious or anxious$ or phobia$ or phobic or panic) adj3 disorder$).ti,ab. 52653
8 or/5-7 105293
9 limit 8 to (english language and yr="2014 -Current") 33716
10 Suicide/ or Attempted Suicide/ or Suicidality/ or Suicidal Ideation/ or exp Self-Injurious Behavior/ 49241
11 (suicid$ or parasuicid$ or self harm$ or Self Injur$).ti. 44620
12 10 or 11 54464
13 limit 12 to (english language and yr="2012 -Current") 22539
14 4 or 9 or 13 108823
15 Screening Tests/ or Psychological Screening Inventory/ or Questionnaires/ or Surveys/ or Self-Report/ 63478
16 (screen$ or self report$).ti. 36565
17 (casefinding or case finding).ti,ab. 755

18 (suicid$ adj3 (scale$ or inventor$ or questionnaire$ or survey$ or index$ or checklist$ or interview$ or screen$ or self report)).ti,ab. 4523
19 ((depress$ or anxiety) adj3 (scale$ or inventor$ or questionnaire$ or survey$ or index$ or checklist$ or interview$ or screen$ or self report)).ti. 6724
20 (Patient Health Questionnaire or PHQ-2 or PHQ-9 or PHQ-ADS).ti,ab. 5071
21 ("Primary Care Evaluation of Mental Disorders" or PRIME-MD).ti,ab. 300
22 ((Center and Epidemiologic and Depression and Scale) or CES-D or CESD$).ti,ab. 5172
23 ("Edinburgh Postpartum Depression Scale" or "Edinburgh Postnatal Depression Scale" or EPDS).ti,ab. 2206
24 ((Geriatric Depression adj2 Scale$) or GDS-15).ti,ab. 3050
25 (Generali?ed Anxiety Disorder Scale or GAD-2 or GAD-7).ti,ab. 1234
26 (Geriatric Anxiety Inventory or GAI-SF).ti,ab. 102
27 (Geriatric Anxiety Scale or GAS-LTC or GAS-10).ti,ab. 35
28 ((Harkavy$ or Asnis$) and suicid$).ti,ab. 19
29 (suicide probability or suicide status form or suicide assessment).ti,ab. 603
30 (paykel$ and suicid$).ti,ab. 37
31 (self harm adj3 (questionnaire$ or scale$ or survey$ or inventory or Manchester)).ti,ab. 257
32 (beck depression and suicid$).ti,ab. 955
33 (hamilton rating and suicid$).ti,ab. 244
34 (symptom driven diagnos$ and suicid$).ti,ab. 3
35 or/15-34 110547
36 Test Sensitivity/ or Test Interpretation/ or Test Specificity/ or Predictive Validity/ or Interrater Reliability/ or Test Sensitivity/ or Test Reliability/ or Psychometrics/ or Error of Measurement/ or Measurement Invariance/ or Test Validity/ 135394
37 (Receiver operat$ or ROC curve$ or sensitivit$ or specificit$ or predictive value or "can be detected" or accuracy or Psychometric$ or false positive$ or false negative$ or miss rate$ or error rate$).ti,ab. 282467
38 36 or 37 365478
39 14 and 35 and 38 3139
40 (((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or ((review adj5 (rationale or evidence)).ti,ab. and "Literature Review".md.) or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("systematic review" or "meta analysis").md. 115132
41 14 and 35 and 40 414
42 39 or 41 3391
43 42 not (Animal not Human).po. 3389
44 limit 43 to (childhood <birth to 12 years> or adolescence <13 to 17 years>) 757
45 limit 43 to adulthood <18+ years> 2603
46 44 not 45 315
47 43 not 46 3074
48 (202109* or 202110* or 202111* or 202112* or 2022*).ch,up. 320754
49 47 and 48 607

Appendix A Table 1. Search Start Dates, by Condition and Key Question

Disorder	KQ1/KQ3	KQ2	KQ4/5: Psychotherapy	KQ4/5: Pharmacotherapy
Depression	*Primary studies* **Search start date:** January 2014 **Rationale:** Bridge from previous review[4]	*ESRs (PHQ, PRIME-MD, CESD, EPDS):* **Search start date:** January 2015 **Rationale:** Abundant ESRs published in past 5 years, earlier systematic reviews likely superseded by more recent reviews *Primary studies (GDS):* **Search start date:** January 2014 **Rationale:** Bridge from Pocklighton 2016[5] (searched thru Apr-2014)	*ESRs:* **Search start date:** January 2015 **Rationale:** Abundant ESRs published in past 5 years, earlier systematic reviews likely superseded by more recent reviews	*ESRs:* **Search start date:** January 2015 **Rationale:** Abundant ESRs published in past 5 years, earlier systematic reviews likely superseded by more recent reviews
Anxiety	**Search start date:** 1990 **Rationale:** First SSRI approved was fluoxetine in 1987, others in early 1990s. Assume no use for anxiety <1990. Very few trials of CBT prior to 1990. Anxiety Disorders Association of America founded in 1990 (believe this was first modern era anxiety-related advocacy group)	*Primary studies (GAD-2/7, EPDS-Anx, GAD, GAI):* **Search start date:** January 2014 **Rationale:** Bridging from other reviews • GAD-7/2: Bridge from Plummer 2016[6] (searched thru Mar-2014) • EPDS-anxiety subscale: Bridge from Sinesi 2019[7] (searched thru Feb-2017) • GAS: Bridge from Balsamo 2018[8] (search dates not provided, most recently published study 2015)	*Primary studies:* **Search start date:** January 2015 **Rationale:** Bridge from Cuijpers 2016[9] (searched thru Aug-2015)	*Primary studies:* **Search start date:** January 2015 **Rationale:** Bridge from: • Slee 2019[10] (searched thru Jul-2017) • Bighelli, 2018[11] (searched thru May-2018) • Imai 2014[12] (Searched thru Jan-2014) • Williams 2017[13] (searched thru Aug-2017)

Appendix A Table 1. Search Start Dates, by Condition and Key Question

Disorder	KQ1/KQ3	KQ2	KQ4/5: Psychotherapy	KQ4/5: Pharmacotherapy
High suicide risk	*Primary studies:* **Search start date:** January 2012 Rationale: Bridge from previous review[14] (searched thru July 2012)	*Primary studies:* **Search start date:** January 2012 Rationale: Bridge from previous review[14] (searched thru July 2012)	*Primary studies:* **Search start date:** January 2012 Rationale: Bridge from previous review[14] (searched thru July 2012)	*Primary studies:* **Search start date:** January 2012 Rationale: Bridge from previous review[14] (searched thru July 2012)

Abbreviations: CBT = cognitive behavioral therapy; CESD = Center for Epidemiologic Studies Depression Scale; EPDS = Edinburgh Postnatal Depression Scale; ESR = existing systematic review; GAD = General Anxiety Disorder Scale; GAI = Geriatric Anxiety Inventory; GAS = Geriatric Anxiety Scale; GDS = Geriatric Depression Scale; KQ = key question; PHQ = Patient Health Questionnaire; PRIME-MD = Primary Care Evaluation of Mental Disorders; SSRI = selective serotonin reuptake inhibitors.

Appendix A Table 2. Inclusion and Exclusion Criteria

	Include	Exclude
Condition definitions	• Major depressive disorder (including depression with peripartum onset or other specifiers). • Anxiety disorders addressed in this review will include generalized anxiety disorder, social anxiety disorder, panic disorder, and anxiety not otherwise specified. • Suicidal ideation includes suicidal thoughts or plan for suicide. • Included studies may address these conditions individually or in combination.	Other mental health disorders (e.g., obsessive-compulsive disorder, posttraumatic stress disorder, psychotic disorders, bipolar disorder, cyclothymia, adjustment disorder with depressed mood, and other depressive disorders [persistent depressive disorder/dysthymia, disruptive mood dysregulation disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition], and other anxiety disorders [agoraphobia, specific phobias, separation anxiety disorder, selective mutism, substance/medication-induced anxiety disorder, anxiety disorder due to another medical condition]).
Population	**KQs 1–3:** Adults (age ≥19 years), including pregnant and postpartum persons. Trials may include: • Unselected primary care population. • Primary care patients without known depression or anxiety disorders or high risk of suicide. • Other comparable broad-based population recruited from a health care setting. **KQs 4, 5:** • Adults (age ≥19 years), including pregnant and postpartum persons, with depressive disorders, anxiety disorders, or high risk of suicide, or with elevated symptoms of depression or anxiety. Sample must include an estimated 50% or more of participants with an included disorder but may also include some participants with related (e.g., other depressive or anxiety disorders) or subsyndromal conditions (e.g., elevated symptoms but not meeting full criteria). • For anxiety and depression, evidence will be limited to studies that recruit primary care patients (or comparable broad-based health care recruitment), although treatment can take place in any outpatient setting, including primary care or specialty care (such as mental health). If evidence in primary care–recruited patients is limited for any condition-by-treatment approach combination, evidence will be extended to patients recruited from other settings.	• Children and adolescents (age ≤18 years). Trials in which >50% of the population are age ≤18 years will be excluded. • Studies limited to populations that are not broadly generalizable to primary care (e.g., persons with specific comorbid mental health conditions such as depression and substance use disorder); persons with other mood disorders (e.g., bipolar disorder, persistent depressive disorder/dysthymia); persons with concomitant medical conditions (e.g., cancer, traumatic brain injury, coronary artery disease, or post-cardiovascular disease event); persons with developmental disorders; persons with physical disabilities; persons in the midst of a suicidal crisis, identified through their presentation for health care services related to self-harm in acute-care settings (i.e., in the emergency department or inpatient setting); persons in residential, institutional, or inpatient settings. • Studies of physician-assisted suicide in patients who are terminally ill.

Appendix A Table 2. Inclusion and Exclusion Criteria

	Include	Exclude
	All KQs: A priori subpopulations of interest include pregnant and postpartum persons, individuals identified through population-based screening in primary care or comparable community settings, and subgroups based on age, sex or gender, race or ethnicity, sexual orientation, and socioeconomic status.	
Interventions	**KQs 1, 3:** Screening interventions with or without additional provider or patient-facing elements such as referral support, treatment guidelines, symptoms monitoring, and standardized treatment. Screening tools must be brief standardized instruments designed to identify persons with depression, anxiety, and/or high risk of suicide (i.e., recent or current suicidal ideation or behavior); self-report, clinician-administered, or electronically delivered (<5 minutes for clinician-administered instruments, <15 minutes for self-administered instruments). **KQ 2:** Limited to the most widely recommended or used screening tools: • For depression: Patient Health Questionnaire (PHQ), 2- and 9-item versions; Center for Epidemiologic Studies Depression Scale (CES-D); Edinburgh Postpartum Depression Scale (EPDS) for perinatal persons; Geriatric Depression Scale (GDS) for older adults. • For anxiety: Generalized Anxiety Disorder scale (GAD), in any form; PHQ Anxiety scale; EPDS-Anxiety subscale, for perinatal persons; Geriatric Anxiety Inventory (GAI) and Geriatric Anxiety Scale (GAS) for older adults. • For anxiety and depression: PHQ-ADS (combines the PHQ and GAD). For suicide screening: Any brief tools. **KQs 4, 5:** Intervention to address depression, anxiety, and/or risk of suicide, including • Counseling (e.g., psychotherapy, psychoeducation, means restriction) • First-line pharmacotherapy agents (selective serotonin reuptake inhibitors [SSRIs], selective serotonin norepinephrine reuptake inhibitors [SNRIs], serotonin modulators (e.g., vortioxetine, vilazodone, nefazodone), atypical agents (e.g., bupropion, mirtazapine), tricyclic antidepressants, buspirone, brexanolone (for postpartum depression only), lithium (for suicide risk only), benzodiazepines (for anxiety only). • Interventions must be conducted in primary care, referable from primary care, or feasible	**KQ 2:** Other screening instruments. **KQs 4, 5:** • Relapse prevention among persons with a history of mood disorders, other treatment modalities (e.g., exercise, light therapy, transcranial magnetic nerve stimulation, electroshock treatment, St. John's wort, social marketing, policy, system-level interventions, or adjunctive agents to enhance the effects of antidepressants) except as optional adjunctive components to first-line approaches. • Intervention involving components that could not be replicated in most health care settings, including environmental components (media message, public signage) or that intervenes on groups in closed (pre-existing) social networks (e.g., in worksites, churches, clubs/teams), or involves potential notification or use of authority figures (e.g., military commanders, workplace supervisors). • Pharmacotherapeutic agents that are not approved by the U.S. Food and Drug Administration for depression or anxiety or are no longer commonly used for anxiety or depression (e.g., monoamine oxidase inhibitors [including reversible monoamine oxidase A inhibitors for anxiety]).

Appendix A Table 2. Inclusion and Exclusion Criteria

	Include	Exclude
	for implementation in a health care setting.	
Comparators	**KQs 1, 3 (Screening):** • Usual care/no screening. • Screening with no feedback of results to providers. **KQ 2 (Diagnostic accuracy):** • Reference standard (structured or semistructured diagnostic interview or a nonbrief [>5 minutes] unstructured interview with mental health clinician) within 2 weeks of screening in populations that include a full spectrum of patient severity for the given setting (i.e., studies cannot limit the patient pool to only nondepressed and known/highly likely depressed patients). Reference conditions include major depressive disorder, generalized anxiety disorder, social anxiety disorder, suicidal ideation, or any combination of the above. **KQs 4, 5 (Counseling):** • Usual care/no intervention. • Waitlist. • Attention control. • Minimal intervention (e.g., usual care limited to no more than 15 minutes of information). **KQs 4, 5 (Pharmacotherapy):** • Placebo (including placebo along with counseling, when compared with the active agent plus the same counseling intervention). • All those listed under "Counseling" above.	Active intervention (i.e., comparative effectiveness).
Outcomes	**KQs 1, 4:** • Depression or anxiety symptoms, remission or diagnosis, or response. • Suicide deaths, self-harm (i.e., suicide attempts), or suicidal ideation. • All-cause mortality. • Quality of life. • Functioning (including vocational). • Change in health status (e.g., improvement in comorbid conditions or reduction in physical complaints). • Pregnancy outcomes (e.g., preterm birth) • Child/infant outcomes (continuation of breastfeeding, achievement of recognized developmental milestones, reduced abuse or neglect). • Emergency department visits or inpatient stays. • Hopelessness.	**KQs 1, 4:** Rate of identification of persons with depression, anxiety, or high risk of suicide (e.g., trials of clinician training to identify persons at high risk of suicide that report no patient outcomes).

Appendix A Table 2. Inclusion and Exclusion Criteria

	Include	Exclude
	KQ 2: Sensitivity, specificity, or data to calculate one or both. **KQs 3, 5:** • Treatment avoidance. • Deterioration in patient-provider relationship. • Labeling stigma, and negative consequences of false positive and false negative test results. • Inappropriate or unnecessary treatment. • Other harms reported by screening and treatment trials. • Paradoxical worsening of mental health symptoms. **KQ 5 (Pharmacotherapy only):** • Serious adverse effects. • Withdrawals due to adverse effects. • Suicidality. • Serotonin syndrome. • Cardiac effects. • Seizures (bupropion only). • Dependence (benzodiazepines only). • Thyroid or renal toxicity (lithium only). • For pregnant persons only: fetal/infant harms (neonatal death, major malformations, small for gestational age/low birth weight, preeclampsia).	
Outcome assessment timing	**KQs 1, 3–5:** ≥6 weeks after baseline, except for suicide death or self-harm (no minimum followup). **KQ 5 (Harms of pharmacotherapy):** No minimum followup. **KQ 2:** Maximum of 2 weeks between screening and reference standard.	
Setting	**KQs 1–3:** • Primary care settings (e.g., internal medicine, family medicine, obstetrics/gynecology, pediatrics [for postpartum screening], family planning, military health clinics, university-based health clinics) or comparable (e.g., identification through health plan administrative databases). • ED setting, if screening is universal rather than targeted to persons presenting with mental health concerns **KQs 4, 5:** • Intervention may be implemented in	**KQs 1–3:** • Community settings. • Mental health clinics (unless recruitment is through primary care screening). • Inpatient settings, residential care facilities, assisted living facilities, adult foster care, or intermediate care facilities (e.g., nursing homes, rehabilitation facilities, subacute care facilities). • Correctional facilities. • Schools (other than school-based health clinics). **KQs 4, 5:** • Correctional facilities.

Appendix A Table 2. Inclusion and Exclusion Criteria

	Include	Exclude
	outpatient health care (primary or specialty, including mental health). • Participants must be recruited from a primary care or comparable broad health care setting. If evidence in these patients is limited, evidence in patients recruited from other low-acuity outpatient settings will be used (e.g., mental health, virtual, or community settings).	• Schools (other than school-based health clinics). • Worksites. • Inpatient/residential facilities (unless identified through primary care-based screening for suicide). • Emergency departments (unless identified through primary care-based screening for suicide).
Study design	**KQs 1, 3:** Randomized, controlled trials; controlled clinical trials **KQ 2:** Systematic reviews and studies of diagnostic accuracy reporting sensitivity and specificity (or comparable statistics) compared with an independently assessed gold standard (structured or semistructured diagnostic interview or a nonbrief [>5 minutes] unstructured interview with mental health clinician) within 2 weeks of screening in populations that include a full spectrum of patient severity for the given setting (i.e., studies cannot limit the patient pool to only nondepressed and known/highly likely depressed patients). **KQ 4:** • Systematic reviews of controlled trials of interventions for depression, comparing active agents with control groups. • Randomized, controlled trials of anxiety interventions in primary care populations. • Systematic reviews of controlled trials of anxiety interventions, comparing active agents with control groups, if primary literature in primary care populations is insufficient. • Randomized, controlled trials of suicide prevention interventions. **KQ 5:** • Randomized, controlled trials of anxiety and suicide prevention interventions in primary care populations. • Systematic reviews of controlled trials comparing active agents with control groups • Systematic reviews of comparative cohort and case-control observational studies • (Harms of pharmacotherapy only): large comparative cohort and case-control observational studies published after identified systematic reviews that include observational studies.	**All KQs:** All other study designs. **KQ 2:** If unable to limit to existing systematic reviews, case-control studies will be used (i.e., studies that limit the study sample to only participants with and without known mental health symptoms).

Appendix A Table 2. Inclusion and Exclusion Criteria

	Include	Exclude
Study geography	Reviews and primary studies that primarily take place in countries categorized as "Very High" on the 2018 Human Development Index (as defined by the United Nations Development Programme) (published 2019).	Reviews in which >50% of included studies take place in countries not categorized as "Very High" on the Human Development Index.
Publication language	English	Any language other than English
Publication year	1980 or later	Prior to 1980
Quality rating	Fair- or good-quality studies	Poor-quality studies

Abbreviations: ED = emergency department; KQ = key question.

Appendix A Table 3. Depression Screening Instruments: PHQ[15]

Prompt: Over the last 2 weeks, how often have you been bothered by any of the following?

Questions	PHQ-9	PHQ-8	PHQ-4	PHQ-2
1. Little interest or pleasure in doing things	X	X	X	X
2. Feeling down, depressed, or hopeless	X	X	X	X
3. Trouble falling or staying asleep, or sleeping too much	X	X		
4. Feeling tired or having little energy	X	X		
5. Poor appetite or overeating	X	X		
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	X	X	X	
7. Trouble concentrating on things, such as reading the newspaper or watching television	X	X		
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	X	X	X	
9. Thoughts that you would be better off dead or of hurting yourself in some way	X			

Score for each question: 0 (not at all), 1 (several days, 2 (more than half the days), 3 (nearly every day)

Abbreviation: PHQ = Patient Health Questionnaire.

Appendix A Table 4. Depression and Suicide Risk Screening Instruments: GDS[16]

Prompt: Select the answer that describes for you felt over the past week.

Questions	GDS-30	GDS-15	GDS-10	GDS-SI
1. Are you basically satisfied with life? (Reverse)	X	X	X	
2. Have you dropped many of your activities and interests?	X	X	X	
3. Do you feel that your life is empty?	X	X	X	X
4. Do you often get bored?	X	X		
5. Are you hopeful about the future? (Reverse)	X			
6. Are you bothered by thoughts you can't get out of your head?	X			
7. Are you in good spirits most of the time? (Reverse)	X	X		
8. Are you afraid that something bad is going to happen?	X	X	X	
9. Do you feel happy most of the time? (Reverse)	X	X	X	X
10. Do you often feel helpless?	X	X	X	
11. Do you often get restless and fidgety?	X			
12. Do you prefer to stay at home rather than go out and do things?	X	X		
13. Do you frequently worry about the future?	X			
14. Do you feel you have more problems with memory than most?	X	X	X	
15. Do you think it is wonderful to be alive now? (Reverse)	X	X		X
16. Do you feel downhearted and blue?	X			
17. Do you feel pretty worthless the way you are now?	X			X
18. Do you worry a lot about the past?	X	X		
19. Do you find life very exciting? (Reverse)	X			
20. Is it hard to get started on new projects?	X			
21. Do you feel full of energy? (Reverse)	X	X	X	
22. Do you feel that your situation is hopeless?	X	X	X	X
23. Do you think most people are better off than you are? (Reverse)	X	X	X	
24. Do you frequently get upset over little things? (Yes, 1)	X			
25. Do you frequently feel like crying? (Yes, 1)	X			
26. Do you have trouble concentrating? (Yes, 1)	X			
27. Do you enjoy getting up in the mornings? (Reverse)	X			
28. Do you prefer to avoid social gatherings? (Yes, 1)	X			
29. Is it easy for you to make decisions? (Reverse)	X			
30. Is your mind as clear as it used to be? (Reverse)	X			

Score for each question: 1 (Yes), 0 (No); unless reverse scoring is noted.

Abbreviations: GDS = Geriatric Depression Scale; GDS-SI = Geriatric Depression Scale – Suicide Ideation.

Appendix A Table 5. Depression Screening Instruments: CES-D[17]

Prompt: Tell me how often have felt this way during the past week.

Questions
1. I was bothered by things that usually don't bother me
2. I did not feel like eating; my appetite was poor
3. I felt that I could not shake off the blues even with help from my family or friends
4. I felt I was just as good as other people
5. I had trouble keeping my mind on what I was doing
6. I felt depressed
7. I felt that everything I did was an effort
8. I felt hopeful about the future
9. I thought my life had been a failure
10. I felt fearful
11. My sleep was restless
12. I was happy
13. I talked less than usual
14. I felt lonely
15. People were unfriendly
16. I enjoyed life
17. I had crying spells
18. I felt sad
19. I felt that people dislike me
20. I could not get "going

Score for each question: 0 (rare or none of the time, <1 day), 1 (some or a little of the time, 1-2 days), 2 (occasionally or a moderate amount of time, 3-4 days), 3 (most or all of the time, 5-7 days)

Abbreviation: CES-D = Center for Epidemiologic Studies Depression Scale.

Appendix A Table 6. Depression Screening Instruments: Whooley[18]

Prompt: Over the past month:

Questions
1. Have you been bothered by feeling down, depressed, or hopeless?
2. Have you been bothered by having little interest or pleasure in doing things?

Scoring: Yes to one or both indicates a positive test

Appendix A Table 7. Depression Screening Instruments: EPDS[19]

Prompt: Please select the answer that comes closest to how you have felt in the past 7 days, not just how you feel today.

Questions	EPDS	EPDS-Anxiety	Scoring
1. I have been able to laugh and see the funny side of things	X		0 (As much as I always could) 1 (Not quite so much now) 2 (Definitely not so much now) 3 (Not at all)
2. I have looked forward with enjoyment to things	X		0 (As much as I ever did) 1 (Rather less than I used to) 2 (Definitely less than I used to) 3 (Hardly at all)
3. I have blamed myself unnecessarily when things went wrong	X	X	3 (Yes, most of the time) 2 (Yes, some of the time) 1 (Not very often) 0 (No, never)
4. I have been anxious or worried for no good reason	X	X	0 (No, not at all) 1 (Hardly ever) 2 (Yes, sometimes) 3 (Yes, very often)
5. I have felt scared or panicky for no very good reason	X	X	3 (Yes, quite a lot) 2 (Yes, sometimes) 1 (No, not much) 0 (No, not at all)
6. Things have been getting on top of me	X		3 (Yes, most of the time I haven't been able to cope at all) 2 (Yes, sometimes I haven't been coping as well as usual) 1 (No, most of the time I have coped quite well) 0 (No, I have been coping as well as ever)
7. I have been so unhappy that I have had difficulty sleeping	X		3 (Yes, most of the time) 2 (Yes, sometimes) 1 (Not very often) 0 (No, not at all)
8. I have felt sad or miserable	X		3 (Yes, most of the time) 2 (Yes, quite often) 1 (Not very often) 0 (No, not at all)
9. I have been so unhappy that I have been crying	X		3 (Yes, most of the time) 2 (Yes, quite often) 1 (Only occasionally) 0 (No, never)
10. The thought of harming myself has occurred to me	X		3 (Yes, quite often) 2 (Sometimes) 1 (Hardly ever) 0 (Never)

Abbreviation: EPDS = Edinburgh Postnatal Depression Scale.

Appendix A Table 8. Depression Screening Instruments: GAD[20]

Prompt: How often have you been bothered by the following over the past 2 weeks?

Questions	GAD-7	GAD-2
1. Feeling nervous, anxious, or on edge	X	X
2. Not being able to stop or control worrying	X	X
3. Worrying too much about different things	X	
4. Trouble relaxing	X	
5. Being so restless that it's hard to sit still	X	
6. Becoming easily annoyed or irritable	X	
7. Feeling afraid as if something awful might happen	X	

Scoring: 3 (nearly every day), 2 (more than half the days), 1 (several days), 0 (not at all)

Abbreviation: GAD = Generalized Anxiety Disorder Scale.

Appendix A Table 9. Anxiety Screening Instruments: PHQ-Panic Disorder[15]

Questions
1. In the last 4 weeks, have you had an anxiety attack—suddenly feeling fear or panic?
2. Has this ever happened before?
3. Do some of these attacks come suddenly out of the blue—that is, in situations where you don't expect to be nervous or uncomfortable?
4. Do these attacks bother you a lot or are you worried about having another attack?
5. During your last bad anxiety attack, did you have symptoms like shortness of breath, sweating, or your heart racing, pounding, or skipping?

Scoring: Yes (1 point) or No (0 points)

Abbreviation: PHQ = Patient Health Questionnaire.

Appendix A Table 10. Anxiety Screening Instruments: GAS[21]

Questions
1. My heart raced or beat strongly.
2. My breath was short.
3. I had an upset stomach.
4. I felt like things were not real or like I was outside of myself.
5. I felt like I was losing control.
6. I was afraid of being judged by others.
7. I was afraid of being humiliated or embarrassed.
8. I had difficulty falling asleep.
9. I had difficulty staying asleep.
10. I was irritable.
11. I had outbursts of anger.
12. I had difficulty concentrating.
13. I was easily startled or upset.
14. I was less interested in doing something I typically enjoy.
15. I felt detached or isolated from others.
16. I felt like I was in a daze.
17. I had a hard time sitting still.
18. I worried too much.
19. I could not control my worry.
20. I felt restless, keyed up, or on edge.
21. I felt tired.
22. My muscles were tense.
23. I had back pain, neck pain, or muscle cramps.
24. I felt like I had no control over my life.
25. I felt like something terrible was going to happen to me.

Scoring: From 0 (not at all) to 3 (all of the time)
NOTE: Development and initial validation of a self-report assessment tool for anxiety among older adults: The Geriatric Anxiety Scale. Daniel L. Segal, Andrea June, Matthew Payne, Frederick L. Coolidge and Brian Yochim. Journal of Anxiety Disorders, 2010-10-01, Volume 24, Issue 7, Pages 709-714.

Abbreviation: GAS = Geriatric Anxiety Scale.

Appendix A Table 11. Suicide Risk Screening Instruments: SDDS-PC[22]

Questions
1. Thoughts of death
2. Wishing you were dead
3. Feeling suicidal

Abbreviation: SDDS-PC = Symptom Driven Diagnostic System for Primary Care.

Appendix A Table 12. Suicide Risk Screening Instruments: Suicide Risk Assessment Tool[23]

Questions	Scoring
1. How much pain are you in?	5-point scale: 1 (no pain)-5 (worst pain ever)
2. How are you coping?	Not well/so, so/well
3. How upset are you?	A lot/a little/Not at all
4. How would you rate your wish to live?	None (0)/Weak (1)/Moderate to strong (2)
5. How would you rate your wish to die?	None (0)/Weak (1)/Moderate to strong (2)
6. Have you been considering suicide in the last month?	Yes/No
7. Have you had a recent loss? (e.g., job loss/change, relationship change, divorce, change of custody of children, death of a loved one, death of a pet, loss of home, forced to move, bankrupty, dismissal from school, legal troubles, etc.)	Yes/No
8. Have you recently abused substances? (e.g., alcohol, sedatives or tranquilizers, stimulants, pain killers, marijuana or hashish, cocaine, club drugs, hallucinogens, opioids, inhalants or solvents, other drugs, etc.)	Yes/No
9. Have you ever attempted to commit suicide?	Yes/No
10. Have you ever been diagnosed with depression or panic, anxiety, or bipolar disorders?	Yes/No
11. Have you ever had a previous inpatient psychiatric hospitalization?	Yes/No

Appendix A Table 13. Study-Design Quality Rating Criteria

Study Design	Adapted Quality Criteria
Cohort studies,* adapted from Newcastle-Ottawa Scale[24]	**Bias arising in randomization process or due to confounding** • Balance in baseline characteristics • No baseline confounding • No time-varying confounding **Bias in selecting participants into the study** • No evidence of biased selection of sample • Start of followup and start of intervention coincide **Bias due to departures form intended interventions** • Participant intervention status is clearly and explicitly defined and measured • Classification of intervention status is unaffected by knowledge of the outcome or risk of the outcome **Bias in classifying interventions** • Fidelity to intervention protocol • Participants were analyzed as originally allocated **Bias from missing data** • Outcome data are reasonably complete and comparable between groups • Confounding variables that are controlled for in analysis are reasonably complete • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** No evidence that the measures, analyses, or subgroup analyses are selectively reported
Randomized clinical trials,* adapted from U.S. Preventive Services Task Force Manual[25]	**Bias arising in the randomization process or due to confounding** • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias in selecting participants into the study** • CCT only: No evidence of biased selection of sample **Bias due to departures from intended interventions** • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated **Bias from missing data** • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** No evidence that the measures, analyses, or subgroup analyses are selectively reported
Diagnostic accuracy, QUADAS-2[26]	**Patient Selection** • Was a consecutive or random sample of patients enrolled • Did the study avoid inappropriate exclusions • Risk of bias: could the selection of patients have introduced bias **Index Test** • Were the index test results interpreted without knowledge of the reference standard results • If a threshold was used, was it pre-specified or was a range of values presented • Risk of bias: Could the conduct or interpretation of the index test have introduced bias **Reference Standard**

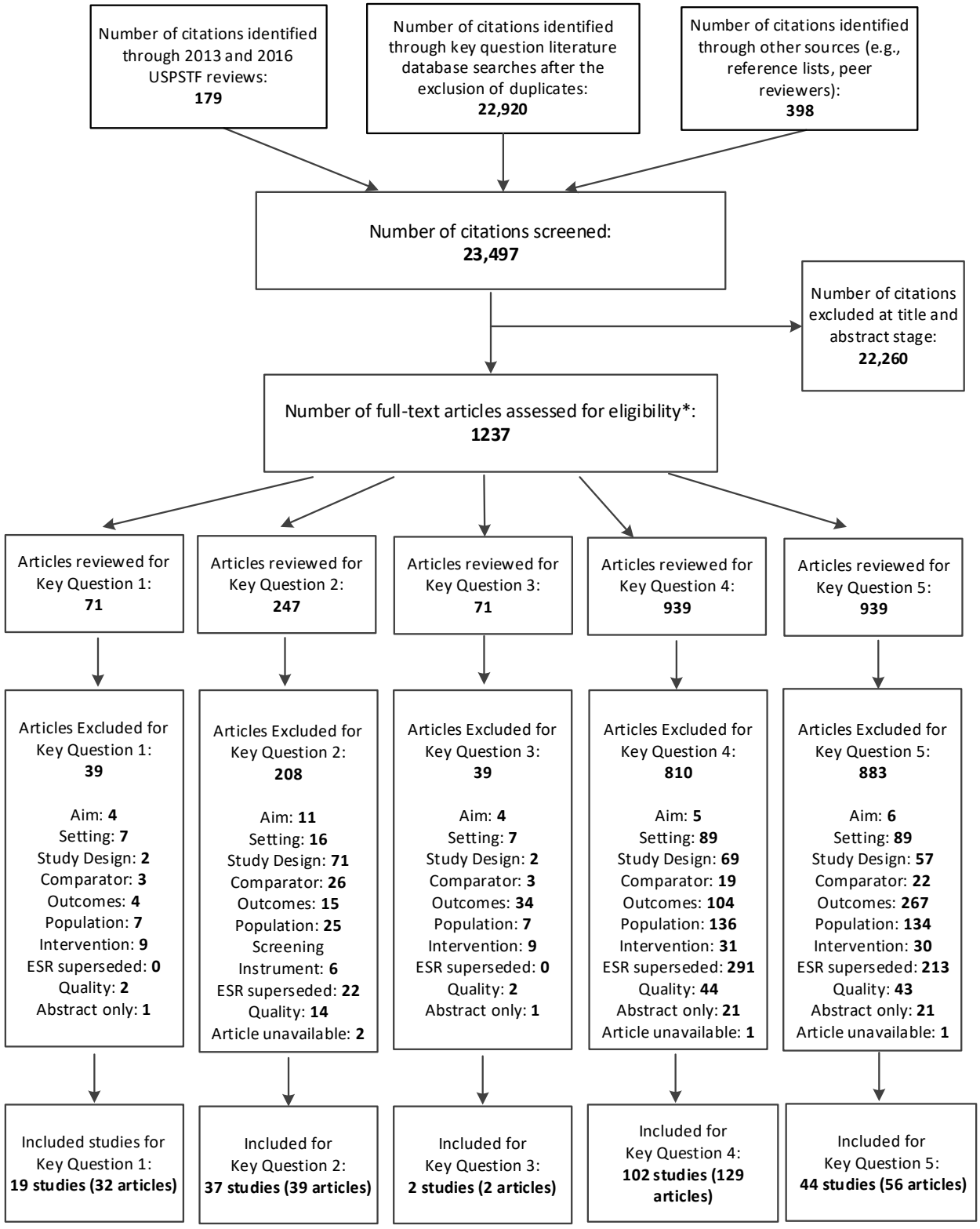
Appendix A Table 13. Study-Design Quality Rating Criteria

Study Design	Adapted Quality Criteria
	• Is the reference standard likely to correctly classify the target condition • Were the reference standard results interpreted without knowledge of the index test • Were staff trained in the use of the reference standard • Was fidelity of the reference standard monitored or reported • Risk of bias: Could the reference standard, its conduct, or its interpretation have introduced bias **Flow and Timing** • Was there an appropriate interval between the index test and reference standard • Did all patients receive a reference standard • Did all patients receive the same reference standard • Were all patients included in the analysis • Risk of bias: Could the patient flow have introduced bias
Systematic reviews,† adapted from U.S. Preventive Services Task Force Manual[25]	**Recency and relevance.** **Comprehensiveness of sources considered, and search strategy used** • Was the Search strategy reported • Were there concerning omissions in the search strategy • Was the search derived from known database with acceptable search strategy **Standardized appraisal of included studies and risk of bias/quality of individual studies** • Were the inclusion criteria explicitly stated • Were the inclusion criteria appropriate for the review questions • Were standardized RoB or quality criteria used in the assessment of individual studies **Validity of conclusions** • Were synthesis methods transparent and nonproblematic • Were conclusions supported by the evidence

*Good-quality studies generally meet all quality criteria. Fair-quality studies do not meet all the criteria but do not have critical limitations that could invalidate study findings. Poor-quality studies have a single fatal flaw or multiple important limitations that could invalidate study findings. Critical appraisal of studies using a priori quality criteria are conducted independently by at least two reviewers. Disagreements in final quality assessment are resolved by consensus, and, if needed, consultation with a third independent reviewer.

†Overall confidence in the results of each review was rated according to published guidance: a rating of "high" reflects that the review had zero or one noncritical weakness; "moderate" indicates the review was judged to have more than one noncritical weakness; "low" means the review was judged to have one critical flaw with or without noncritical weaknesses or multiple noncritical weaknesses; and "critically low" signifies that more than one critical flaw was present.

Appendix B Figure 1. Literature Flow Diagram



*Studies may appear in more than one Key Question.

Appendix C List 1. Included evidence for Depression, by Key Question (KQ)

Ancillary publication(s) indented under primary article

KQs 1 and 3: Included studies for screening benefits and harms, by author

Bergus GR, Hartz AJ, Noyes R, Jr., et al. The limited effect of screening for depressive symptoms with the PHQ-9 in rural family practices. J Rural Health. 2005;21(4):303-9. PMID: 16294652. https://doi.org/10.1111/j.1748-0361.2005.tb00099.x

Bijl D, van Marwijk HWJ, Ader HJ, et al. A randomised controlled trial to improve the recognition, diagnosis and treatment of major depression in elderly people in general practice - primary and secondary outcomes of the West Friesland Study. Diemen: College Voor Zortgverskeringen; 2003.

> Bosmans J, de Bruijne M, van Hout H, et al. Cost-effectiveness of a diseaes management program for major depression in elderly primary care patients. Journal of general internal medicine. 2006;21(10):1020-6. PMID: 16836625. https://doi.org/10.1111/j.1525-1497.2006.00555.x

Callahan CM, Hendrie HC, Dittus RS, et al. Improving treatment of late life depression in primary care: a randomized clinical trial. J Am Geriatr Soc. 1994;42(8):839-46. PMID: 8046193. https://doi.org/10.1111/j.1532-5415.1994.tb06555.x

Glavin K, Smith L, Sorum R, et al. Redesigned community postpartum care to prevent and treat postpartum depression in women--a one-year follow-up study. J Clin Nurs. 2010;19(21-22):3051-62. PMID: 20726926. https://doi.org/10.1111/j.1365-2702.2010.03332.x

> Glavin K, Smith L, Sorum R, et al. Supportive counselling by public health nurses for women with postpartum depression. J Adv Nurs. 2010;66(6):1317-27. PMID: 20384641. https://doi/10.1111/j.1365-2648.2010.05263.x

Jarjoura D, Polen A, Baum E, et al. Effectiveness of screening and treatment for depression in ambulatory indigent patients. Journal of general internal medicine. 2004;19(1):78-84. PMID: 14748864. https://doi.org/10.1111/j.1525-1497.2004.21249.x

Kroenke K, Talib TL, Stump TE, et al. Incorporating PROMIS Symptom Measures into Primary Care Practice-a Randomized Clinical Trial. Journal of general internal medicine. 2018;33(8):1245-52. PMID: 29623512. https://dx.doi.org/10.1007/s11606-018-4391-0

Leung SS, Leung C, Lam TH, et al. Outcome of a postnatal depression screening programme using the Edinburgh Postnatal Depression Scale: a randomized controlled trial. J Public Health (Oxf). 2011;33(2):292-301. PMID: 20884642. https://doi.org/10.1093/pubmed/fdq075

MacArthur C, Winter HR, Bick DE, et al. Effects of redesigned community postnatal care on womens' health 4 months after birth: a cluster randomised controlled trial. Lancet (London, England). 2002;359(9304):378-85. PMID: 11844507. https://doi.org/10.1016/s0140-6736(02)07596-7

Morrell CJ, Slade P, Warner R, et al. Clinical effectiveness of health visitor training in psychologically informed approaches for depression in postnatal women: pragmatic cluster randomised trial in primary care. BMJ (Clinical research ed). 2009;338:a3045. PMID: 19147636. https://doi.org/10.1136/bmj.a3045

- Morrell CJ, Warner R, Slade P, et al. Psychological interventions for postnatal depression: cluster randomised trial and economic evaluation. The PONDER trial. Health Technol Assess. 2009;13(30):1-176. PMID: 19555590. https://doi.org/10.3310/hta13300

Rost K, Nutting P, Smith J, et al. Improving depression outcomes in community primary care practice: a randomized trial of the quEST intervention. Quality Enhancement by Strategic Teaming. Journal of general internal medicine. 2001;16(3):143-9. PMID: 11318908. https://doi.org/10.1111/j.1525-1497.2001.00537.x

Rost K, Nutting P, Smith JL, et al. Managing depression as a chronic disease: a randomised trial of ongoing treatment in primary care. BMJ (Clinical research ed). 2002;325(7370):934. PMID: 12399343. https://doi.org/10.1136/bmj.325.7370.934

Rost K, Nutting PA, Smith J, et al. Designing and implementing a primary care intervention trial to improve the quality and outcome of care for major depression. General hospital psychiatry. 2000;22(2):66-77. PMID: 10822094. https://doi.org/10.1016/s0163-8343(00)00059-1

van der Weele GM, de Waal MW, van den Hout WB, et al. Effects of a stepped-care intervention programme among older subjects who screened positive for depressive symptoms in general practice: the PROMODE randomised controlled trial. Age Ageing. 2012;41(4):482-8. PMID: 22427507. https://doi.org/10.1093/ageing/afs027

van der Zee-van den Berg AI, Boere-Boonekamp MM, Groothuis-Oudshoorn CG, et al. Post-up study: Postpartum depression screening in well-child care and maternal outcomes. Pediatrics. 2017;140(4):1-8. PMID: 28882876. https://doi.org/10.1542/peds.2017-0110

van der Weele GM, de Waal MW, van den Hout WB, et al. Yield and costs of direct and stepped screening for depressive symptoms in subjects aged 75 years and over in general practice. Int J Geriatr Psychiatry. 2011;26(3):229-38. PMID: 20665554. https://doi.org/10.1002/gps.2518

Wells KB, Sherbourne C, Schoenbaum M, et al. Impact of disseminating quality improvement programs for depression in managed primary care: A randomized controlled trial. JAMA. 2000;283(2):212-20. PMID: 10634337. https://doi.org/10.1001/jama.283.2.212

Sherbourne CD, Wells KB, Duan N, et al. Long-term effectiveness of disseminating quality improvement for depression in primary care. Archives of general psychiatry. 2001;58(7):696-703. PMID: 11448378. https://doi.org/10.1001/archpsyc.58.7.696

Wells K, Sherbourne C, Schoenbaum M, et al. Five-year impact of quality improvement for depression: Results of a group-level randomized controlled trial. Archives of general psychiatry. 2004;61(4):378-86. PMID: 15066896. https://doi.org/10.1001/archpsyc.61.4.378

Whooley M, Stone B. Randomized trial of case-finding for depression in elderly primary care patients. Journal of general internal medicine. 2000;15(5):293-300. PMID: 10840264. https://doi.org/10.1046/j.1525-1497.2000.04319.x

Wickberg B, Tjus T, Hwang P. Using the EPDS in routine antenatal care in Sweden: a naturalistic study. J Reprod Infant Psychol. 2005;23(1):33-41. https://doi.org/10.1080/02646830512331330956

Williams J, CD M, Kroenke K. Case-finding for depression in primary care: A randomized trial. The American journal of medicine. 1999;106(1):36-43. PMID: 10320115. https://doi.org/10.1016/s0002-9343(98)00371-4

Yawn BP, Dietrich AJ, Wollan P, et al. TRIPPD: a practice-based network effectiveness study of postpartum depression screening and management. Annals of family medicine. 2012;10(4):320-9. PMID: 22778120. https://doi.org/10.1370/afm.1418

Yawn BP, Bertram S, Kurland M, et al. Repeated depression screening during the first postpartum year. Annals of family medicine. 2015;13(3):228-34. PMID: 25964400. https://dx.doi.org/10.1370/afm.1777

KQ 2: Included studies for test accuracy, by study design

Primary research studies

Alves Apostolo JL, Bobrowicz-Campos EM, Carvalho dos Reis IA, et al. Exploring the screening capacity of the European Portuguese version of the 15-item Geriatric Depression Scale. Revista de Psicopatologia y Psicologia Clinica. 2018;23(2):99-107. http://dx.doi.org/10.5944/rppc.vol.23.num.2.2018.21050

Blank K, Gruman C, Robison JT. Case-finding for depression in elderly people: balancing ease of administration with validity in varied treatment settings. J Gerontol A Biol Sci Med Sci. 2004;59(4):378-84. PMID: 15071082. https://doi.org/10.1093/gerona/59.4.m378

Broekman BF, Niti M, Nyunt MS, et al. Validation of a brief seven-item response bias-free geriatric depression scale. Am J Geriatr Psychiatry. 2011;19(6):589-96. PMID: 21606902. https://doi.org/10.1097/JGP.0b013e3181f61ec9

Davison TE, McCabe MP, Mellor D. An examination of the "gold standard" diagnosis of major depression in aged-care settings. Am J Geriatr Psychiatry. 2009;17(5):359-67. PMID: 19390293. https://doi.org/10.1097/JGP.0b013e318190b901

Eriksen S, Bjorklof GH, Helvik AS, et al. The validity of the hospital anxiety and depression scale and the geriatric depression scale-5 in home-dwelling old adults in Norway. Journal of affective disorders. 2019;256:380-5. PMID: 31212233. https://dx.doi.org/10.1016/j.jad.2019.05.049

Izal M, Montorio I, Nuevo R, et al. Optimising the diagnostic performance of the Geriatric Depression Scale. Psychiatry Res. 2010;178(1):142-6. PMID: 20452060. https://doi.org/10.1016/j.psychres.2009.02.018

Jung YE, Kim MD, Bahk WM, et al. Validation of the Korean Version of the Depression in Old Age Scale and Comparison with Other Depression Screening Questionnaires Used in Elderly Patients in Medical Settings. Clin. 2019;17(3):369-76. PMID: 31352703. https://dx.doi.org/10.9758/cpn.2019.17.3.369

Licht-Strunk E, van der Kooij KG, van Schaik DJ, et al. Prevalence of depression in older patients consulting their general practitioner in The Netherlands. Int J Geriatr Psychiatry. 2005;20(11):1013-9. PMID: 16250082. https://doi.org/10.1002/gps.1391

Marc LG, Raue PJ, Bruce ML. Screening performance of the 15-item geriatric depression scale in a diverse elderly home care population. Am J Geriatr Psychiatry. 2008;16(11):914-21. PMID: 18978252. https://doi.org/10.1097/JGP.0b013e318186bd67

Pellas J, Damberg M. Accuracy in detecting major depressive episodes in older adults using the Swedish versions of the GDS-15 and PHQ-9. Ups J Med Sci. 2021;126. PMID: 34754407. https://dx.doi.org/10.48101/ujms.v126.7848

Rait G, Burns A, Baldwin R, et al. Screening for depression in African-Caribbean elders. Fam Pract. 1999;16(6):591-5. PMID: 10625132. https://doi.org/10.1093/fampra/16.6.591

Shin C, Park MH, Lee SH, et al. Usefulness of the 15-item geriatric depression scale (GDS-15) for classifying minor and major depressive disorders among community-dwelling elders. Journal of affective disorders. 2019;259:370-5. PMID: 31470180. https://dx.doi.org/10.1016/j.jad.2019.08.053

Stefan AM, Baban A. The Romanian version of the Geriatric Depression Scale: Reliability and validity. Cognition, Brain, Behavior: An Interdisciplinary Journal. 2017;21(3):175-87. http://dx.doi.org/10.24193/cbb.2017.21.10

van Marwijk HW, Wallace P, de Bock GH, et al. Evaluation of the feasibility, reliability and diagnostic value of shortened versions of the geriatric depression scale. The British journal of general practice : the journal of the Royal College of General Practitioners. 1995;45(393):195-9. PMID: 7612321.

ESRs

Bosanquet K, Bailey D, Gilbody S, et al. Diagnostic accuracy of the Whooley questions for the identification of depression: a diagnostic meta-analysis. BMJ Open. 2015;5(12):e008913. PMID: 26656018. https://dx.doi.org/10.1136/bmjopen-2015-008913

Harel D, Levis B, Sun Y, et al. External validation of a shortened screening tool using individual participant data meta-analysis: A case study of the Patient Health Questionnaire-Dep-4. Methods. 2022;204:300-11. PMID: 34780986. https://dx.doi.org/10.1016/j.ymeth.2021.11.005

He C, Levis B, Riehm KE, et al. The Accuracy of the Patient Health Questionnaire-9 Algorithm for Screening to Detect Major Depression: An Individual Participant Data Meta-Analysis. Psychother Psychosom. 2020;89(1):25-37. PMID: 31593971. https://dx.doi.org/10.1159/000502294

Levis B, Negeri Z, Sun Y, et al. Accuracy of the Edinburgh Postnatal Depression Sscale (EPDS) for Screening to Detect Major Depression among Pregnant and Postpartum Women: Systematic Review and Meta-analysis of Individual Participant Data. BMJ (Clinical research ed). 2020;371:m4022. PMID: 33177069. https://doi.org/10.1136/bmj.m4022

Levis B, Sun Y, He C, et al. Accuracy of the PHQ-2 Alone and in Combination With the PHQ-9 for Screening to Detect Major Depression: Systematic Review and Meta-analysis. JAMA. 2020;323(22):2290-300. PMID: 32515813. https://dx.doi.org/10.1001/jama.2020.6504

Negeri ZF, Levis B, Sun Y, et al. Accuracy of the Patient Health Questionnaire-9 for screening to detect major depression: updated systematic review and individual participant data meta-analysis. BMJ (Clinical research ed). 2021;375:n2183. PMID: 34610915. https://dx.doi.org/10.1136/bmj.n2183

Smith RD, Shing JSY, Lin J, et al. Meta-analysis of diagnostic properties of the Whooley questions to identify depression in perinatal women. Journal of affective disorders. 2022;315:148-55. PMID: 35931230. https://dx.doi.org/10.1016/j.jad.2022.07.026

Vilagut G, Forero CG, Barbaglia G, et al. Screening for Depression in the General Population with the Center for Epidemiologic Studies Depression (CES-D): A Systematic Review with Meta-Analysis. PLoS ONE [Electronic Resource]. 2016;11(5):e0155431. PMID: 27182821. https://dx.doi.org/10.1371/journal.pone.0155431

Wang, L., Kroenke, K., Stump, T. E., & Monahan, P. O. (2021). Screening for perinatal depression with the Patient Health Questionnaire depression scale (PHQ-9): A systematic review and meta-analysis. *Gen Hosp Psychiatry, 68*, 74-82. PMID: 33360526. https://dx.doi.org/10.1016/j.genhosppsych.2020.12.007.

Wu Y, Levis B, Riehm KE, et al. Equivalency of the diagnostic accuracy of the PHQ-8 and PHQ-9: a systematic review and individual participant data meta-analysis. Psychol Med. 2019:1-13. PMID: 31298180. https://dx.doi.org/10.1017/S0033291719001314

KQs 4-5: Included ESRs for treatment benefits and harms, by intervention type

Psychological interventions

Aherne D, Fitzgerald A, Aherne C, et al. Evidence for the treatment of moderate depression: a systematic review. Ir J Psychol Med. 2017;34(3):197-204. PMID: 30115148. https://dx.doi.org/10.1017/ipm.2017.10

Castro A, Gili M, Ricci-Cabello I, et al. Effectiveness and adherence of telephone-administered psychotherapy for depression: A systematic review and meta-analysis. Journal of affective disorders. 2020;260:514-26. PMID: 31539688. https://dx.doi.org/10.1016/j.jad.2019.09.023

Collado A, Lim AC, MacPherson L. A systematic review of depression psychotherapies among Latinos. Clin Psychol Rev. 2016;45:193-209. PMID: 27113679. https://dx.doi.org/10.1016/j.cpr.2016.04.001

Cuijpers P. Four decades of outcome research on psychotherapies for adult depression: An overview of a series of meta-analyses. Canadian Psychology/Psychologie canadienne. 2017;58(1):7-19. http://dx.doi.org/10.1037/cap0000096

Cuijpers P, Karyotaki E, de Wit L, et al. The effects of fifteen evidence-supported therapies for adult depression: A meta-analytic review. Psychother. 2020;30(3):279-93. PMID: 31394976. https://dx.doi.org/10.1080/10503307.2019.1649732

Cuijpers P, Karyotaki E, Reijnders M, et al. Was Eysenck right after all? A reassessment of the effects of psychotherapy for adult depression. Epidemiol Psychiatr Sci. 2019;28(1):21-30. PMID: 29486804. https://doi.org/10.1017/s2045796018000057

Cuijpers P, Karyotaki E, Reijnders M, et al. Who benefits from psychotherapies for adult depression? A meta-analytic update of the evidence. Cognitive Behav Ther. 2018;47(2):91-106. PMID: 29345530. https://dx.doi.org/10.1080/16506073.2017.1420098

Cuijpers P, Quero S, Papola D, et al. Care-as-usual control groups across different settings in randomized trials on psychotherapy for adult depression: a meta-analysis. Psychol Med. 2019:1-11. PMID: 31843031. https://dx.doi.org/10.1017/S0033291719003581

Cuijpers P, Reijnders M, Karyotaki E, et al. Negative effects of psychotherapies for adult depression: A meta-analysis of deterioration rates. Journal of affective disorders. 2018;239:138-45. PMID: 30005327. https://dx.doi.org/10.1016/j.jad.2018.05.050

Driessen E, Hollon SD, Bockting CL, et al. Does Publication Bias Inflate the Apparent Efficacy of Psychological Treatment for Major Depressive Disorder? A Systematic Review and Meta-Analysis of US National Institutes of Health-Funded Trials. PLoS ONE [Electronic Resource]. 2015;10(9):e0137864. PMID: 26422604. https://dx.doi.org/10.1371/journal.pone.0137864

Ebert DD, Donkin L, Andersson G, et al. Does Internet-based guided-self-help for depression cause harm? An individual participant data meta-analysis on deterioration rates and its moderators in randomized controlled trials. Psychol Med. 2016;46(13):2679-93. PMID: 27649340. https://dx.doi.org/10.1017/S0033291716001562

Harerimana B, Forchuk C, O'Regan T. The use of technology for mental healthcare delivery among older adults with depressive symptoms: A systematic literature review. Int J Ment Health Nurs. 2019;28(3):657-70. PMID: 30666762. https://dx.doi.org/10.1111/inm.12571

Harper Shehadeh M, Heim E, Chowdhary N, et al. Cultural Adaptation of Minimally Guided Interventions for Common Mental Disorders: A Systematic Review and Meta-Analysis. JMIR Ment Health. 2016;3(3):e44. PMID: 27670598. https://dx.doi.org/10.2196/mental.5776

Holvast F, Massoudi B, Oude Voshaar RC, et al. Non-pharmacological treatment for depressed older patients in primary care: A systematic review and meta-analysis. PLoS ONE [Electronic Resource]. 2017;12(9):e0184666. PMID: 28938015. https://dx.doi.org/10.1371/journal.pone.0184666

Huang L, Zhao Y, Qiang C, et al. Is cognitive behavioral therapy a better choice for women with postnatal depression? A systematic review and meta-analysis. PLoS ONE [Electronic Resource]. 2018;13(10):e0205243. PMID: 30321198. https://dx.doi.org/10.1371/journal.pone.0205243

Jonsson U, Bertilsson G, Allard P, et al. Psychological Treatment of Depression in People Aged 65 Years and Over: A Systematic Review of Efficacy, Safety, and Cost-Effectiveness. PLoS ONE [Electronic Resource]. 2016;11(8):e0160859. PMID: 27537217. https://dx.doi.org/10.1371/journal.pone.0160859

Karyotaki E, Kemmeren L, Riper H, et al. Is self-guided internet-based cognitive behavioural therapy (iCBT) harmful? An individual participant data meta-analysis. Psychol Med. 2018;48(15):2456-66. PMID: 29540243. https://doi.org/10.1017/s0033291718000648

Karyotaki E, Ebert DD, Donkin L, et al. Do guided internet-based interventions result in clinically relevant changes for patients with depression? An individual participant data meta-analysis. Clin Psychol Rev. 2018;63:80-92. PMID: 29940401. https://doi.org/10.1016/j.cpr.2018.06.007

Karyotaki E, Riper H, Twisk J, et al. Efficacy of Self-guided Internet-Based Cognitive Behavioral Therapy in the Treatment of Depressive Symptoms: A Meta-analysis of Individual Participant Data. JAMA Psychiatry. 2017;74(4):351-9. PMID: 28241179. https://doi.org/10.1001/jamapsychiatry.2017.0044

Letourneau NL, Dennis CL, Cosic N, et al. The effect of perinatal depression treatment for mothers on parenting and child development: A systematic review. Depress Anxiety. 2017;34(10):928-66. PMID: 28962068. https://dx.doi.org/10.1002/da.22687

Li X, Laplante DP, Paquin V, et al. Effectiveness of cognitive behavioral therapy for perinatal maternal depression, anxiety and stress: A systematic review and meta-analysis of randomized controlled trials. Clin Psychol Rev. 2022;92:102129. PMID: 35123346. https://dx.doi.org/10.1016/j.cpr.2022.102129

Massoudi B, Holvast F, Bockting CLH, et al. The effectiveness and cost-effectiveness of e-health interventions for depression and anxiety in primary care: A systematic review and meta-analysis. Journal of affective disorders. 2019;245:728-43. PMID: 30447572. https://dx.doi.org/10.1016/j.jad.2018.11.050

Nair U, Armfield NR, Chatfield MD, et al. The effectiveness of telemedicine interventions to address maternal depression: A systematic review and meta-analysis. Journal of Telemedicine & Telecare. 2018;24(10):639-50. PMID: 30343660. https://dx.doi.org/10.1177/1357633X18794332

Nieuwenhuijsen K, Verbeek JH, Neumeyer-Gromen A, et al. Interventions to improve return to work in depressed people. Cochrane Database Syst Rev. 2020;10:CD006237. PMID: 33052607. https://doi.org/10.1002/14651858.CD006237.pub4

Pineros-Leano M, Liechty JM, Piedra LM. Latino immigrants, depressive symptoms, and cognitive behavioral therapy: A systematic review. Journal of affective disorders. 2017;208:567-76. PMID: 27810273. https://dx.doi.org/10.1016/j.jad.2016.10.025

Ponting C, Mahrer NE, Zelcer H, et al. Psychological interventions for depression and anxiety in pregnant Latina and Black women in the United States: A systematic review. Clinical Psychology & Psychotherapy. 2020;27(2):249-65. PMID: 31960525. https://dx.doi.org/10.1002/cpp.2424

Rojas-Garcia A, Ruiz-Perez I, Rodriguez-Barranco M, et al. Healthcare interventions for depression in low socioeconomic status populations: A systematic review and meta-analysis. Clin Psychol Rev. 2015;38:65-78. PMID: 25797906. https://dx.doi.org/10.1016/j.cpr.2015.03.001
Also included under depression pharmacologic interventions

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Rojas-Garcia A, Ruiz-Perez I, Rodriguez-Barranco M, et al. Healthcare interventions for depression in low socioeconomic status populations: A systematic review and meta-analysis. Clin Psychol Rev. 2015;38:65-78. PMID: 25797906. https://dx.doi.org/10.1016/j.cpr.2015.03.001

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Wang YC, Tai PA, Poly TN, et al. Increased Risk of Dementia in Patients with Antidepressants: A Meta-Analysis of Observational Studies. Behav. 2018;2018:5315098. PMID: 30123386. https://dx.doi.org/10.1155/2018/5315098

Appendix C List 2. Included evidence for anxiety, by KQ

Ancillary publication(s) indented under primary article

KQs 1 and 3: Included studies for screening benefits and harms, by author

Mathias SD, Fifer SK, Mazonson PD, et al. Necessary but not sufficient: the effect of screening and feedback on outcomes of primary care patients with untreated anxiety. Journal of general internal medicine. 1994;9(11):606-15. PMID: 7853069. http://doi.org/10.1007/BF02600303

Fifer S, Mathias S, Patrick D, et al. Untreated anxiety among adult primary care patients in a Health Maintenance Organization. Archives of general psychiatry. 1994;51(9):740-50.

Yelin E, Mathias SD, Buesching DP, et al. The impact on unemployment of an intervention to increase recognition of previously untreated anxiety among primary care physicians. Soc Sci Med. 1996;42(7):1069-75. PMID: 8730912. https://doi.org/10.1016/0277-9536(95)00297-9

Kroenke K, Talib TL, Stump TE, et al. Incorporating PROMIS Symptom Measures into Primary Care Practice-a Randomized Clinical Trial. Journal of general internal medicine. 2018;33(8):1245-52. PMID: 29623512. https://dx.doi.org/10.1007/s11606-018-4391-0

KQ 2: Included studies for test accuracy, by author

Ahn JK, Kim Y, Choi KH. The Psychometric Properties and Clinical Utility of the Korean Version of GAD-7 and GAD-2. Front Psychiatr. 2019;10:127. PMID: 30936840. https://dx.doi.org/10.3389/fpsyt.2019.00127

Austin MV, Mule V, Hadzi-Pavlovic D, et al. Screening for anxiety disorders in third trimester pregnancy: a comparison of four brief measures. Arch Women Ment Health. 2021;05:05. PMID: 34350480. https://dx.doi.org/10.1007/s00737-021-01166-9

Gould CE, Segal DL, Yochim BP, et al. Measuring anxiety in late life: a psychometric examination of the geriatric anxiety inventory and geriatric anxiety scale. Journal of Anxiety Disorders. 2014;28(8):804-11. PMID: 25271176. https://dx.doi.org/10.1016/j.janxdis.2014.08.001

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Makulowich AA. Identification of patients with anxiety symptoms in an integrated community care clinic among a predominantly Latino patient population. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2019;80(1-B(E)):No Pagination Specified.

Matthey S, Valenti B, Souter K, et al. Comparison of four self-report measures and a generic mood question to screen for anxiety during pregnancy in English-speaking women. Journal of affective disorders. 2013;148(2-3):347-51. PMID: 23380518. https://doi.org/10.1016/j.jad.2012.12.022

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KQs 4-5: Included studies for treatment benefits and harms, by study design

Anxiety Primary studies

Psychological interventions

Burger H, Verbeek T, Aris-Meijer JL, et al. Effects of psychological treatment of mental health problems in pregnant women to protect their offspring: randomised controlled trial. Br J Psychiatry. 2020;216(4):182-8. PMID: 31806071. https://dx.doi.org/10.1192/bjp.2019.260

Clark DM, Wild J, Warnock-Parkes E, et al. More than doubling the clinical benefit of each hour of therapist time: a randomised controlled trial of internet cognitive therapy for social anxiety disorder. Psychol Med. 2022:1-11. PMID: 35835726. https://dx.doi.org/10.1017/S0033291722002008

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Fletcher J, Lovell K, Bower P, et al. Process and Outcome of a Non-Guided Self-Help Manual for Anxiety and Depression in Primary Care: A Pilot Study. Behav. 2005;33(3):319-31. https://dx.doi.org/10.1017/S1352465805002079

Gensichen J, Hiller TS, Breitbart J, et al. Panic Disorder in Primary Care. Dtsch. 2019;116(10):159-66. PMID: 30995952. https://dx.doi.org/10.3238/arztebl.2019.0159

Brettschneider C, Gensichen J, Hiller TS, et al. Cost-effectiveness of Practice Team-Supported Exposure Training for Panic Disorder and Agoraphobia in Primary Care: a Cluster-Randomized Trial. Journal of general internal medicine. 2020;35(4):1120-6. PMID: 31965532. https://dx.doi.org/10.1007/s11606-020-05658-9

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Lenox-Smith AJ, Reynolds A. A double-blind, randomised, placebo controlled study of venlafaxine XL in patients with generalised anxiety disorder in primary care. Br J Gen Pract. 2003;53(495):772-7. PMID: 14601352.

Lenze EJ, Rollman BL, Shear MK, et al. Escitalopram for older adults with generalized anxiety disorder: a randomized controlled trial. Jama. 2009;301(3):295-303. PMID: 19155456. http://doi.org/10.1001/jama.2008.977

Sheehy O, Zhao JP, Berard A. Association Between Incident Exposure to Benzodiazepines in Early Pregnancy and Risk of Spontaneous Abortion. JAMA Psychiatry. 2019;15:15. PMID: 31090881. https://dx.doi.org/10.1001/jamapsychiatry.2019.0963

Vera M, Oben A, Juarbe D, et al. Randomized pilot trial of cognitive-behavioral therapy and acceptance-based behavioral therapy in the treatment of Spanish-speaking Latino primary care patients with generalized anxiety disorder. Journal of Behavioral and Cognitive Therapy. 2021;31(2):91-103. http://dx.doi.org/10.1016/j.jbct.2020.11.007

Appendix C. Included Studies Lists

Anxiety ESRs

Psychological interventions

Cuijpers P, Cristea IA, Karyotaki E, et al. How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. World psychiatry : official journal of the World Psychiatric Association (WPA). 2016;15(3):245-58. PMID: 27717254. http://doi.org/10.1002/wps.20346

Cuijpers P, Cristea IA, Weitz E, et al. The effects of cognitive and behavioural therapies for anxiety disorders on depression: a meta-analysis. Psychol Med. 2016;46(16):3451-62. PMID: 27659840. http://doi.org/10.1017/S0033291716002348

Gould RL, Coulson MC, Howard RJ. Efficacy of cognitive behavioral therapy for anxiety disorders in older people: a meta-analysis and meta-regression of randomized controlled trials. J Am Geriatr Soc. 2012;60(2):218-29. PMID: 22283717. http://doi.org/10.1111/j.1532-5415.2011.03824.x

Hofmann SG, Wu JQ, Boettcher H. Effect of cognitive-behavioral therapy for anxiety disorders on quality of life: a meta-analysis. J Consult Clin Psychol. 2014;82(3):375-91. PMID: 24447006. http://doi.org/10.1037/a0035491

Li X, Laplante DP, Paquin V, et al. Effectiveness of cognitive behavioral therapy for perinatal maternal depression, anxiety and stress: A systematic review and meta-analysis of randomized controlled trials. Clin Psychol Rev. 2022;92:102129. PMID: 35123346. https://dx.doi.org/10.1016/j.cpr.2022.102129

van Dis EAM, van Veen SC, Hagenaars MA, et al. Long-term Outcomes of Cognitive Behavioral Therapy for Anxiety-Related Disorders: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2020;77(3):265-73. PMID: 31758858. https://dx.doi.org/10.1001/jamapsychiatry.2019.3986

Ponting C, Mahrer NE, Zelcer H, et al. Psychological interventions for depression and anxiety in pregnant Latina and Black women in the United States: A systematic review. Clinical Psychology & Psychotherapy. 2020;27(2):249-65. PMID: 31960525. https://dx.doi.org/10.1002/cpp.2424

Weaver A, Himle JA. Cognitive-behavioral therapy for depression and anxiety disorders in rural settings: A review of the literature. Journal of Rural Mental Health. 2017;41(3):189-221. PMID: 31004323. http://dx.doi.org/10.1037/rmh0000075

Pharmacological interventions

Imai H, Tajika A, Chen P, et al. Azapirones versus placebo for panic disorder in adults. Cochrane Database Syst Rev. 2014(9). http://doi.org/10.1002/14651858.CD010828.pub2

Roest AM, de Jonge P, Williams CD, et al. Reporting Bias in Clinical Trials Investigating the Efficacy of Second-Generation Antidepressants in the Treatment of Anxiety Disorders: A Report of 2 Meta-analyses. JAMA Psychiatry. 2015;72(5):500-10. PMID: 25806940. https://dx.doi.org/10.1001/jamapsychiatry.2015.15

Slee A, Nazareth I, Bondaronek P, et al. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet (London, England). 2019;393(10173):768-77. PMID: 30712879. https://doi.org/10.1016/S0140-6736(18)31793-8

Williams T, Hattingh CJ, Kariuki CM, et al. Pharmacotherapy for social anxiety disorder (SAnD). Cochrane Database Syst Rev. 2017;10:CD001206. PMID: 29048739. https://dx.doi.org/10.1002/14651858.CD001206.pub3

Viswanathan M. Maternal, Fetal, and Child Outcomes of Mental Health Treatments in Women: A Meta-Analysis of Perinatal Pharmacotherapy. 2021.

Appendix C List 3. Included evidence for suicide risk, by KQ

Ancillary publication(s) indented under primary article

KQs 1 and 3: Included studies for screening benefits and harms

Crawford MJ, Thana L, Methuen C, et al. Impact of screening for risk of suicide: randomised controlled trial. Br J Psychiatry. 2011;198:379-84. PMID: 21525521. https://doi.org/10.1192/bjp.bp.110.083592

KQ 2: Included studies for test accuracy, by study design

Desjardins I, Cats-Baril W, Maruti S, et al. Suicide Risk Assessment in Hospitals: An Expert System-Based Triage Tool. Journal of Clinical Psychiatry. 2016;77(7):e874-82. PMID: 27314465. https://dx.doi.org/10.4088/JCP.15m09881

Heisel MJ, Duberstein PR, Lyness JM, et al. Screening for suicide ideation among older primary care patients. Journal of the American Board of Family Medicine : JABFM. 2010;23(2):260-9. PMID: 20207936. https://doi.org/10.3122/jabfm.2010.02.080163

Olfson M, Weissman MM, Leon AC, et al. Suicidal ideation in primary care. Journal of general internal medicine. 1996;11(8):447-53. PMID: 8872781. https://doi.org/10.1007/bf02599038

KQs 4-5: Included studies for treatment benefits and harms, by author

Borschmann R, Barrett B, Hellier JM, et al. Joint crisis plans for people with borderline personality disorder: feasibility and outcomes in a randomised controlled trial. Br J Psychiatry. 2013;202(5):357-64. PMID: 23637110. https://doi.org/10.1192/bjp.bp.112.117762

Bruce ML, Ten Have TR, Reynolds CF, III, et al. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized controlled trial. JAMA. 2004;291(9):1081-91. PMID: 14996777. https://doi.org/10.1001/jama.291.9.1081

> Alexopoulos GS, Reynolds CF, III, Bruce ML, et al. Reducing suicidal ideation and depression in older primary care patients: 24-month outcomes of the PROSPECT study. Am J Psychiatry. 2009;166(8):882-90. PMID: 19528195. https://doi.org/10.1176/appi.ajp.2009.08121779
>
> Bao Y, Alexopoulos GS, Casalino LP, et al. Collaborative depression care management and disparities in depression treatment and outcomes. Archives of General Psychiatry2011. p. 627-36. PMID: 21646579. https://doi.org/10.1001/archgenpsychiatry.2011.55
>
> Bogner HR, Joo JH, Hwang S, et al. Does a Depression Management Program Decrease Mortality in Older Adults with Specific Medical Conditions in Primary Care? An Exploratory Analysis. J Am Geriatr Soc. 2016;64(1):126-31. PMID: 26782861. https://dx.doi.org/10.1111/jgs.13711
>
> Bogner HR, Morales KH, Post EP, et al. Diabetes, depression, and death: a randomized controlled trial of a depression treatment program for older adults based in primary care (PROSPECT). Diabetes Care. 2007;30(12):3005-10. PMID: 17717284. https://doi.org/10.2337/dc07-0974

Byers AL, Bruce ML, Raue P. Suicidal ideation in non-depressed elderly primary care patients: The PROSPECT Study. Am J Geriatr Psychiatry. 2009;17:A86.

Coyne JC, Koppel J, Colenda CC, et al. Interventions for treatment of depression in primary care. JAMA. 2004;291(23):2814-6. PMID: 15199023. https://doi.org/10.1001/jama.291.23.2814-a

Gallo JJ, Bogner HR, Morales KH, et al. The effect of a primary care practice-based depression intervention on mortality in older adults: a randomized trial. Ann Intern Med. 2007;146(10):689-98. PMID: 17502629. https://doi.org/10.7326/0003-4819-146-10-200705150-00002

Thombs BD, Ziegelstein RC. Diabetes, depression, and death: a randomized controlled trial of a depression treatment program for older adults based in primary care (PROSPECT): response to Bogner et al. Diabetes Care. 2008;31(6):e54-e. PMID: 18509141. https://doi.org/10.2337/dc08-0446

Bush NE, Smolenski DJ, Denneson LM, et al. A Virtual Hope Box: Randomized Controlled Trial of a Smartphone App for Emotional Regulation and Coping With Distress. Psychiatr Serv. 2017;68(4):330-6. https://doi.org/10.1176/appi.ps.201600283

Carter GL, Willcox CH, Lewin TJ, et al. Hunter DBT project: randomized controlled trial of dialectical behaviour therapy in women with borderline personality disorder. Aust N Z J Psychiatry. 2010;44(2):162-73. PMID: 20113305. https://doi.org/10.3109/00048670903393621

Davidson K, Norrie J, Tyrer P, et al. The effectiveness of cognitive behavior therapy for borderline personality disorder: results from the borderline personality disorder study of cognitive therapy (BOSCOT) trial. J Pers Disord. 2006;20(5):450-65. PMID: 17032158. https://doi.org/10.1521/pedi.2006.20.5.450

Franklin JC, Fox KR, Franklin CR, et al. A brief mobile app reduces nonsuicidal and suicidal self-injury: Evidence from three randomized controlled trials. J Consult Clin Psychol. 2016;84(6):544-57. https://doi.org/10.1037/ccp0000093

Goodman M, Banthin D, Blair NJ, et al. A Randomized Trial of Dialectical Behavior Therapy in High-Risk Suicidal Veterans. Journal of Clinical Psychiatry. 2016;77(12):e1591-e600. PMID: 27780335. https://dx.doi.org/10.4088/JCP.15m10235

Jobes D, Comtois K, Gutierrez P, et al. A Randomized Controlled Trial of the Collaborative Assessment and Management of Suicidality versus Enhanced Care as Usual With Suicidal Soldiers. Psychiatry (new york). 2017;80(4):339-56. https://doi.org/10.1080/00332747.2017.1354607

Katz IR, Rogers MP, Lew R, et al. Lithium Treatment in the Prevention of Repeat Suicide-Related Outcomes in Veterans With Major Depression or Bipolar Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2022;79(1):24-32. PMID: 34787653. https://dx.doi.org/10.1001/jamapsychiatry.2021.3170

Kovac SH, Range LM. Does writing about suicidal thoughts and feelings reduce them? Suicide & life-threatening behavior. 2002;32(4):428-40. PMID: 12501967. https://doi.org/10.1521/suli.32.4.428.22335

Linehan MM, Comtois KA, Murray AM, et al. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. Archives of general psychiatry. 2006;63(7):757-66. PMID: 16818865. https://doi.org/10.1001/archpsyc.63.7.757

Harned MS, Jackson SC, Comtois KA, et al. Dialectical behavior therapy as a precursor to PTSD treatment for suicidal and/or self-injuring women with borderline personality disorder. Journal of Traumatic Stress2010. p. 421-9. PMID: 20648564. https://doi.org/10.1002/jts.20553

Reynolds SK, Lindenboim N, Comtois KA, et al. Risky assessments: participant suicidality and distress associated with research assessments in a treatment study of suicidal behavior. Suicide Life Threat Behav. 2006;36(1):19-34. PMID: 16676622. https://doi.org/10.1521/suli.2006.36.1.19

McMain SF, Guimond T, Barnhart R, et al. A randomized trial of brief dialectical behaviour therapy skills training in suicidal patients suffering from borderline disorder. Acta Psychiatr Scand. 2017;135(2):138-48. PMID: 27858962. https://dx.doi.org/10.1111/acps.12664

Muhlmann C, Madsen T, Hjorthoj C, et al. Effectiveness of an Internet-Based Self-help Therapy Program for Suicidal Ideation With Follow-up at 6 Months: Results of a Randomized Controlled Trial. Journal of Clinical Psychiatry. 2021;82(5):31. PMID: 34464522. https://dx.doi.org/10.4088/JCP.20m13803

Pigeon WR, Funderburk JS, Cross W, et al. Brief CBT for insomnia delivered in primary care to patients endorsing suicidal ideation: a proof-of-concept randomized clinical trial. Transl Behav Med. 2019;9(6):1169-77. PMID: 31271210. https://dx.doi.org/10.1093/tbm/ibz108

Pistorello J, Fruzzetti AE, Maclane C, et al. Dialectical behavior therapy (DBT) applied to college students: a randomized clinical trial. J Consult Clin Psychol. 2012;80(6):982-94. PMID: 22730955. https://dx.doi.org/10.1037/a0029096

Pistorello J, Jobes DA, Gallop R, et al. A Randomized Controlled Trial of the Collaborative Assessment and Management of Suicidality (CAMS) Versus Treatment as Usual (TAU) for Suicidal College Students. Arch. 2021;25(4):765-89. PMID: 32275480. https://dx.doi.org/10.1080/13811118.2020.1749742

Priebe S, Bhatti N, Barnicot K, et al. Effectiveness and cost-effectiveness of dialectical behaviour therapy for self-harming patients with personality disorder: a pragmatic randomised controlled trial. Psychother Psychosom. 2012;81(6):356-65. PMID: 22964561. https://dx.doi.org/10.1159/000338897

Barnicot K, Savill M, Bhatti N, et al. A pragmatic randomised controlled trial of dialectical behaviour therapy: effects on hospitalisation and post-treatment follow-up. Psychother Psychosom. 2014;83(3):192-3. PMID: 24752222. https://dx.doi.org/10.1159/000357365

Riblet NB, Kenneally L, Stevens S, et al. A virtual, pilot randomized trial of a brief intervention to prevent suicide in an integrated healthcare setting. General hospital psychiatry. 2022;75:68-74. PMID: 35202942. https://dx.doi.org/10.1016/j.genhosppsych.2022.02.002

Simon GE, Shortreed SM, Rossom RC, et al. Effect of Offering Care Management or Online Dialectical Behavior Therapy Skills Training vs Usual Care on Self-harm Among Adult Outpatients With Suicidal Ideation: A Randomized Clinical Trial. JAMA. 2022;327(7):630-8. PMID: 35166800. https://dx.doi.org/10.1001/jama.2022.0423

Torok M, Han J, McGillivray L, et al. The effect of a therapeutic smartphone application on suicidal ideation in young adults: Findings from a randomized controlled trial in Australia. PLoS Med. 2022;19(5):e1003978. PMID: 35639672. https://dx.doi.org/10.1371/journal.pmed.1003978

Van Orden KA, Arean PA, Conwell Y. A Pilot Randomized Trial of Engage Psychotherapy to Increase Social Connection and Reduce Suicide Risk in Later Life. Am J Geriatr Psychiatry. 2021;29(8):789-800. PMID: 33952416. https://dx.doi.org/10.1016/j.jagp.2021.03.009

van Spijker B, van Straten A, Kerkhof A. Effectiveness of online self-help for suicidal thoughts: results of a randomised controlled trial. PloS one. 2014;9(2):e90118. PMID: 24587233. https://dx.doi.org/10.1371/journal.pone.0090118

Ward-Ciesielski EF, Tidik JA, Edwards AJ, et al. Comparing brief interventions for suicidal individuals not engaged in treatment: A randomized clinical trial. Journal of affective disorders. 2017;222:153-61. PMID: 28709022. https://dx.doi.org/10.1016/j.jad.2017.07.011

Ward-Ciesielski EF. An open pilot feasibility study of a brief dialectical behavior therapy skills-based intervention for suicidal individuals. Suicide & life-threatening behavior. 2013;43(3):324-35. PMID: 23409778. https://doi.org/10.1111/sltb.12019

Reason for Exclusion*
E1. Aim
E1a. Not an included condition
E2. Setting
E2a. Not conducted in very high HDI country
E3. Study design
E3a. Original research covered by an ESR
E3b. Development sample only (KQ2)
E4. Comparator
E5. Outcomes (no relevant outcomes)
E6. Outcome assessment timing
E7. Population
E7a. Primarily limited to an excluded population
E7b. Not limited to a primary care population but otherwise meets inclusion criteria
E8. Intervention
E9a. Not an included screening instrument (but addressed a target condition)
E9b. Not a relevant screening instrument (addressed an excluded condition)
E10a. ESR superseded by another ESR
E11. Poor quality
E12. Non-English
E13. Unable to locate article
E14. Abstract only or study ongoing, no outcomes published
E15. Interval between screener and ref std > 2 weeks

*Assigned at full-text phase

Abbreviations: E = exclude

KQs 1 and 3 Excluded Studies

1. Ahmad, F, Lou, W, et al. Preconsult interactive computer-assisted client assessment survey for common mental disorders in a community health centre: a randomized controlled trial. CMAJ open. 5(1): E190-E197. 2017. PMID: 28401134. dx.doi.org/10.9778/cmajo.20160118 **KQ1E5, KQ3E5**
2. Almeida, OP, Pirkis, J, et al. A randomized trial to reduce the prevalence of depression and self-harm behavior in older primary care patients. Ann Fam Med. 10(4): 347-356. 2012. PMID: 22778123. **KQ1E1, KQ3E1**
3. Anding, J, Rohrle, B, et al. Early Detection of Postpartum Depressive Symptoms in Mothers and Fathers and Its Relation to Midwives' Evaluation and Service Provision: A Community-Based Study. Frontiers in Pediatrics. 3: 62. 2015. PMID: 26217649. dx.doi.org/10.3389/fped.2015.00062 **KQ1E1, KQ3E1**
4. Bender, TheodoreW, Fitzpatrick, Skye, et al. Does it hurt to ask? An analysis of iatrogenic risk during suicide risk assessment. Neurol Psychol Brain Res. 33: 73-81. 2019. **KQ1E2, KQ3E2**
5. Bender, TW. Screening for Suicide in an Adult Population: An Analysis of Iatrogenic Risk. Psychology. Doctor of Philosophy. 2012. **KQ1E2, KQ3E2**
6. Boudreaux, ED, Camargo, CA, et al. Improving Suicide Risk Screening and Detection in the Emergency Department. Am J Prev Med. 50(4): 445-453. 2016. PMID: 26654691. dx.doi.org/10.1016/j.amepre.2015.09.029 **KQ1E5, KQ3E5**

7. Byatt, N, Brenckle, L, et al. Improving perinatal depression care in obstetric settings: pRogram in Support of Moms (PRISM). Arch Womens Ment Health. 22(5): 702. 2019. **KQ1E14, KQ3E14**
8. de Beurs, DP, Ghoncheh, R, et al. Psychological Distress Because of Asking about Suicidal Thoughts: A Randomized Controlled Trial among Students. Archives of Suicide Research. 20(2): 153-9. 2016. PMID: 25751130. dx.doi.org/10.1080/13811118.2015.1004475 **KQ1E2, KQ3E2**
9. Edward, KL, Giandinoto, JA, et al. Self-screening using the Edinburgh post natal depression scale for mothers and fathers to initiate early help seeking behaviours. Arch Psychiatr Nurs. 33(4): 421-427. 2019. PMID: 31280789. dx.doi.org/10.1016/j.apnu.2019.05.007 **KQ1E11, KQ3E11**
10. Fletcher, S, Spittal, MJ, et al. Clinical efficacy of a Decision Support Tool (Link-me) to guide intensity of mental health care in primary practice: a pragmatic stratified randomised controlled trial. The Lancet. Psychiatry. 8(3): 202-214. 2021. dx.doi.org/10.1016/S2215-0366(20)30517-4 **KQ1E4, KQ3E4**
11. Gidding, LG, Spigt, M, et al. PsyScan e-tool to support diagnosis and management of psychological problems in general practice: a randomised controlled trial. Br J Gen Pract. 68(666): e18-e27. 2018. PMID: 29255109. dx.doi.org/10.3399/bjgp17X694109 **KQ1E7, KQ3E7**
12. Gould, MS, Marrocco, FA, et al. Evaluating iatrogenic risk of youth suicide screening programs: a randomized controlled trial. JAMA. 293(13): 1635-1643. 2005. PMID: 15811983. **KQ1E7a, KQ3E7a**
13. Gould, MS, Marrocco, FA, et al. Service use by at-risk youths after school-based suicide screening. J Am Acad Child Adolesc Psychiatry. 48(12): 1193-1201. 2009. PMID: 19858758. **KQ1E7a, KQ3E7a**
14. Harris, KM, Goh, MT. Is suicide assessment harmful to participants? Findings from a randomized controlled trial. Int J Ment Health Nurs. 26(2): 181-190. 2017. https://dx.doi.org/10.1111/inm.12223 **KQ1E2, KQ3E2**
15. Kigozi, J, Jowett, S, et al. Cost-Utility Analysis of Routine Anxiety and Depression Screening in Patients Consulting for Osteoarthritis: Results From a Clinical, Randomized Controlled Trial. Arthritis Care Res (Hoboken). 70(12): 1787-1794. 2018. PMID: 29609205. dx.doi.org/10.1002/acr.23568 **KQ1E7a, KQ3E7a**
16. King, CA, Eisenberg, D, et al. Online suicide risk screening and intervention with college students: a pilot randomized controlled trial. J Consult Clin Psychol. 83(3): 630-6. 2015. **KQ1E2, KQ3E2**
17. Kleinveld, JH, Timmermans, DR, et al. Does prenatal screening influence anxiety levels of pregnant women? A longitudinal randomised controlled trial. Prenat Diagn. 26(4): 354-61. 2006. PMID: 16511902. **KQ1E1, KQ3E1**
18. Law, Mary Kate, Furr, Michael R, et al. Does assessing suicidality frequently and repeatedly cause harm? A randomized control study. Psychol Assess. 27(4): 1171-1181. 2015. https://dx.doi.org/10.1037/pas0000118 **KQ1E8, KQ3E8**
19. Mathias, CW, Michael Furr, R, et al. What's the harm in asking about suicidal ideation?. Suicide Life Threat Behav. 42(3): 341-51. 2012. https://dx.doi.org/10.1111/j.1943-278X.2012.0095.x **KQ1E7a, KQ3E7a**
20. Meyers, MA, Groh, CJ, et al. Depression screening and treatment in

uninsured urban patients. Journal of the American Board of Family Medicine: JABFM. 27(4): 520-9. 2014. PMID: 25002006. dx.doi.org/10.3122/jabfm.2014.04.130254 **KQ1E4, KQ3E4**

21. Ono, Y, Sakai, A, et al. Effectiveness of a multimodal community intervention program to prevent suicide and suicide attempts: a quasi-experimental study. PLoS ONE [Electronic Resource]. 8(10): e74902. 2013. PMID: 24130673. dx.doi.org/10.1371/journal.pone.0074902 **KQ1E8, KQ3E8**
22. Oyama, H, Sakashita, T. Community-based screening intervention for depression affects suicide rates among middle-aged Japanese adults. Psychol Med. 47(8): 1500-1509. 2017. **KQ1E8, KQ3E8**
23. Oyama, H, Sakashita, T. Differences in specific depressive symptoms among community-dwelling middle-aged Japanese adults before and after a universal screening intervention. Soc Psychiatry Psychiatr Epidemiol. 49(2): 251-8. 2014. **KQ1E8, KQ3E8**
24. Oyama, H, Sakashita, T. Effects of universal screening for depression among middle-aged adults in a community with a high suicide rate. J Nerv Ment Dis. 202(4): 280-6. 2014. **KQ1E8, KQ3E8**
25. Oyama, H, Sakashita, T, et al. A community-based survey and screening for depression in the elderly: the short-term effect on suicide risk in Japan. Crisis. 31(2): 100-8. 2010. PMID: 20418216. doi.org/10.1027/0227-5910/a000007 **KQ1E8, KQ3E8**
26. Oyama, H, Sakashita, T. Long-Term Effects of a Screening Intervention for Depression on Suicide Rates among Japanese Community-Dwelling Older Adults. American Journal of Geriatric Psychiatry. 24(4): 287-96. 2016. PMID: 26796924. dx.doi.org/10.1016/j.jagp.2015.10.008 **KQ1E8, KQ3E8**
27. Picardi, A, Lega, I, et al. A randomised controlled trial of the effectiveness of a program for early detection and treatment of depression in primary care. J Affect Disord. 198: 96-101. 2016. **KQ1E1, KQ3E1**
28. Robinson, J, Pan, YuenH, et al. Does screening high school students for psychological distress, deliberate self-harm, or suicidal ideation cause distress--and is it acceptable? An Australian-based study. Crisis. 32: 254-263. 2011. **KQ1E7a, KQ3E7a**
29. Rona, Rj, Burdett, H, et al. Post-deployment screening for mental disorders and tailored advice about help-seeking in the UK military: a cluster randomised controlled trial. Lancet. (no pagination). 2017. **KQ1E7, KQ3E7**
30. Silverstone, PH, Rittenbach, K, et al. Depression Outcomes in Adults Attending Family Practice Were Not Improved by Screening, Stepped-Care, or Online CBT during a 12-Week Study when Compared to Controls in a Randomized Trial. Frontiers in psychiatry Frontiers Research Foundation. 8: 32. 2017. PMID: 28373846. dx.doi.org/10.3389/fpsyt.2017.00032 **KQ1E11, KQ3E11**
31. Smith, Phillip, Poindexter, Erin, et al. The Effect of Participating in Suicide Research: Does Participating in a Research Protocol on Suicide and Psychiatric Symptoms Increase Suicide Ideation and Attempts?. Suicide Life Threat Behav. 40(6): 535-543. 2010. doi.org/10.1521/suli.2010.40.6.535 **KQ1E8, KQ3E8**
32. Staeheli, M, Aseltine, RH, et al. Using mHealth technologies to improve the identification of behavioral health problems in urban primary care settings. SAGE Open Medicine. 5:

2050312117712656. 2017. PMID: 28634539. dx.doi.org/10.1177/2050312117712656 **KQ1E5, KQ3E5**

33. Swavely, D, O'Gurek, DT, et al. Primary Care Practice Redesign: Challenges in Improving Behavioral Health Care for a Vulnerable Patient Population. American Journal of Medical Quality. 35(2): 101-109. 2020. PMID: 31226884. dx.doi.org/10.1177/1062860619855136 **KQ1E3, KQ3E3**
34. Thomas, HV, Lewis, G, et al. Computerised patient-specific guidelines for management of common mental disorders in primary care: a randomised controlled trial. Br J Gen Pract. 54(508): 832-7. 2004. PMID: 15527609. **KQ1E8, KQ3E8**
35. Thombs, BD, Markham, S, et al. Does depression screening in primary care improve mental health outcomes?. BMJ. 374: n1661. 2021. dx.doi.org/10.1136/bmj.n1661 **KQ1E3, KQ3E3**
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KQs 4-5 Excluded Studies

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Appendix E Table 1. Participant Characteristics of Depression Screening Studies (KQ1)

Author, Year	Target Pop	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	% Screen Pos	BL MH Status
Bergus, 2005[27]	General adults	41 (NR)	66.7	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: NR	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: 94.1	13.8	Medication for depression or anxiety: 38%
Bijl, 2003[28]	Older adults	65.6 (55+)	57.2	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: Education none-low: 65%	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	17.2	NR
Callahan, 1994[29]	Older adults	65.3 (NR)	75.9	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: NR	Black: 51.2 Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	16.2	Depression dx in medical chart: 20.8% Antidepressants: 11.5% Alcohol dependency, CAGE score ≥2: 13.8%
Glavin, 2010[30]	Perinatal	32.5 (≥18)	100 (Postpartum)	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: NR	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	10.1	NR
Jarjoura, 2004[31]	General adults	45 (24-67)	68.9	High school grad: NR College grad: NR High school grad: NR College grad: NR	Employed: Single: Other SES: Medicaid or uninsured + below poverty line: 100%	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	45.4	Treatment for depression: 0%

Appendix E Table 1. Participant Characteristics of Depression Screening Studies (KQ1)

Author, Year	Target Pop	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	% Screen Pos	BL MH Status
Kroenke, 2018[32]	General adults	49.4 (NR)	71.7	High school grad: NR College grad: 13.3	Employed: NR Single: NR Other SES: Edu high school or less: 53.3%	Black: 49.3 Latinx: NR Asian/AA: NR Native Am/AN: NR White: 45.0	89	t-score ≥55 on PROMIS depression subscale: 59.3% t-score ≥55 on PROMIS anxiety subscale: 72.3%
Leung, 2011[33]	Perinatal	NR (NR)	100 (Postpartum)	High school grad: NR College grad: NR	Employed: 57.4 Single: 4.5 Other SES: Family income ≤HK$19,999: 50.4%	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	25.1	NR
MacArthur, 2002[34]	Perinatal	NR (NR)	100 (Postpartum)	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: Deprived Townsend quartile: 24.4%; Most deprived Townsend quartile: 24.4%	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	NR	NR
Morrell, 2009[35]	Perinatal	NR (≥18)	100 (Postpartum)	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: Living with partner: 93.8%; Rent council or housing association: 14.4%	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: 95.3%	17.3	EPDS ≥12: 15.2%
Rost, 2001[36]	General adults	42.6 (≥18)	83.9	High school grad: 79.1 College grad: NR	Employed: 55.5 Single: Other SES: Health insurance: 84.1%; Income	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: 84.3	5.9	NR

Appendix E Table 1. Participant Characteristics of Depression Screening Studies (KQ1)

Author, Year	Target Pop	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	% Screen Pos	BL MH Status
					(mean) $10,408			
van der Weele, 2012[37]	Older adults	80 (≥75)	72.4	High school grad: NR College grad: NR	Employed: Single: Other SES: Income only social security: 16.7%; Living independently: 71.5%; Living alone: 64.4%	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	5.5	MDD: 15% Treatment for depression: 0% >14 drinks/wk alcohol: 9.6%
van der Zee, 2017[38]	Perinatal	30.7 (NR)	100 (Postpartum)	High school grad: NR College grad: NR	Employed: 82.5 Single: NR Other SES: NR	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	6.6	Lifetime depression: 19.8%
Wells, 2000[39]	General adults	43.7 (≥18)	70.7	High school grad: 29.7 College grad: 19.9	Employed: NR Single: NR Other SES: NR	Black: 7.1 Latinx: 29.6 Asian/AA: NR Native Am/AN: NR White: 57.0	14.3	MDD: 41.4% Any anxiety disorder: 43.3% Antidepressants: 27.4% Alcohol abuse: 7%
Whooley, 2000[40]	Older adults	75.8 (≥65)	60.7	High school grad: 81.1 College grad: NR	Employed: NR Single: NR Other SES: NR	Black: 32.6 Latinx: 4.5 Asian/AA: 7.5 Native Am/AN: NR White: 43.9	14.1	Antidepressants, past 12 mo: 19.9%
Wickberg, 2005[41]	Perinatal	NR (NR)	100 (Pregnant)	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: NR	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	13.9	EPDS ≥12: 13.9%

Appendix E Table 1. Participant Characteristics of Depression Screening Studies (KQ1)

Author, Year	Target Pop	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	% Screen Pos	BL MH Status
Williams, 1999[42]	General adults	58 (≥18)	71	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: Edu (yrs, median): 11; Annual income <$7200: 39.3% Annual income $7200-16799: 36.4% Annual income >=16800: 24.3%	Black: 10.4 Latinx: 59.3 Asian/AA: NR Native Am/AN: NR White: 29	37.1	MDD: 8.0% Panic disorder or GAD: 4.1% Alcohol abuse: 15.2%
Yawn, 2012[43]	Perinatal	26.4 (≥18)	100 (Postpartum)	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: Living with a partner: 75.7%; Income >$50,000: 37.1%; Uninsured at 2mo postpartum: 36.8%	Black: 18 Latinx: 12 Asian/AA: NR Native Am/AN: NR White: NR	27.9	NR

*Gender was not reported in studies of perinatal patients so participants are counted as women, recognizing that there may be some individuals who do not identify as women; non-binary/gender non-conforming categories were not reported in any studies.

Abbreviations: Asian/AA = Asian/Asian American; BL = baseline; CAGE score = Cut, Annoyed, Guilty, and Eye; dx = diagnosis; EPDS = Edinburgh Postnatal Depression Scale; GAD = generalized anxiety disorder; MDD = major depressive disorder; MH = mental health; Native Am/AN = Native American/Alaska Native; NR = not reported; pos = positive; PROMIS = Patient Reported Outcomes Measurement Information System; SES = socioeconomic status.

Appendix E Table 2. Intervention Description of Depression Screening Studies (KQ1)

Author, Year	IG	Intervention detail	Adherence	Acceptability
Bergus, 2005[27]	IG1	Medical providers of control subjects were not informed of the PHQ-9 results. Providers of intervention subjects were asked to review the completed PHQ-9, which made them aware of the subjects' self-reported severity of depression symptoms. All the providers were educated about the PHQ-9 but were not otherwise influenced to change their practices	NR	Physicians reported the instrument was useful in 18 (78%) of these 23 baseline visits
Bijl, 2003[28]	IG1	4-hour training session covering screening, diagnosis, and treatment of depression. GPs were instructed to provide education, information, drug therapy, and supportive contact to patient. Based on Dutch depression guideline (van Marwijk, 1994). GPs completed diagnostic interview using PRIME-MD when notified patient had screened positive on GDS. Patient enrolled and treated if GP assigned MDD diagnosis. Treatment guidelines consisted of education and information, drug therapy, and supportive counseling. The treatment was divided into two phases: an acute treatment phase, in which the patients had to return every 2 weeks for a period of 2 months, and a continued treatment phase, in which the patients had to return every month for a period of 4 months. The total treatment lasted for 6 months. Recommended drug therapy was 20 mg paroxetine daily. For supportive counseling, the patient and the GP together decided in consultation on one specific problem, which bothered the patient. A practical problem was to be chosen, because it was not the intention to include more reflective forms of psychotherapy.	NR	NR
Callahan, 1994[29]	IG1	Three additional appointments to their primary care physicians were scheduled for intervention patients over 3 months. These occurred immediately after the first extended interview and immediately after the interviews at 1 and 3 months. The patient's medical record was supplemented by the intervention materials, which included an educational flyer for the patient, feedback of the patient's HAM-D score and its interpretation, previous HAM-D scores, and a list of currently prescribed medications that have been associated with depression. The primary care physicians, using this information in addition to his/her own clinical history and examination, made the determination of whether the patient would benefit from therapy for depression. Clinicians received a letter for	NR	NR

Appendix E Table 2. Intervention Description of Depression Screening Studies (KQ1)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		each patient that contained a clinical algorithm detailing the initiation, management, and monitoring of antidepressant medications in elderly patients. General recommendations were to discontinue medications associated with depression (a list of such medications was provided, with alternatives); nortriptyline or imiprimine were recommended first-line agents if medications were initiated, with fluoxetine as a 2nd-line agent. After 3 intervention visits, physicians were asked to complete a brief questionnaire concerning their clinical decision making for that particular patient.		
Glavin, 2010[30]	IG1	A the standard 2-weeks postpartum home visit by the public health nurse (PHN), there was an increased focus on maternal mental health (e.g., brochure) and mothers were informed about study. Mothers were enrolled in the study at the 6 weeks' postpartum visit. At this session, the EPDS was administered and all women were given a supportive counseling session by the PHN (20-min session w/active listening and emphatic communication). Subsequently, supportive counseling was provided by the PHN for the depressed mothers (30 min per session, number of sessions was individualized). PHNs were trained to encourage openness about mental health issues at every clinic visit and system for referral to further treatment in the municipality was implemented. Nurses received 5 days of training about postpartum depression w/monthly supervision by psychologists. The training program consisted of: (i) learning about PPD as a phenomenon, risk factors, symptoms, and treatment; (ii) identification of mental health problems among new mothers; (iii) becoming familiar with EPDS forms and the scoring of these in combination with clinical judgment to identify postpartum mothers with depressive symptoms; (iv) training in supportive counselling methods. Some main elements were emphasized in the counselling: (i) Listen and try to understand how things are from the woman's point of view, (ii) Check your understanding of the situation with the woman if unsure, (iii) Treat the woman with the utmost respect and consideration, (iv) Be self-aware, self-accepting, and open with the woman.	NR	NR

Appendix E Table 2. Intervention Description of Depression Screening Studies (KQ1)

Author, Year	IG	Intervention detail	Adherence	Acceptability
Jarjoura, 2004[31]	IG1	Screening nurse gave residents screening results and provided treatment protocol outline asking them to: (1) explore sx with the pt to affirm screen results; (2) attempt to rule out physical conditions, medications, or other primary psychiatric dx that could explain the results; and (3) do the following if a depression diagnosis was appropriate: (a) educate pt about depression, (b) give pt materials, (c) encourage behavioral treatment at partner agency, (d) discuss antidepressants and decide if appropriate, (e) schedule appt in 4 wks, and (f) ensure pts sees nurse for referral info/help. Nurse arranged behavioral tx appointment if desired, or instructions to make an appointment. Nurse faxed pt information to behavioral tx provider. All residents were trained to follow AHRQ depression tx guidelines. Medications provided for free.	NR	NR
Leung, 2011[33]	IG1	EPDS used to identify pts w/postnatal depression; those w/scores ≥9/10 or suicidal ideation (positive answer to question 10) offered non-directive counseling by nurses or management by the community psychiatric team as appropriate (as were those in the CG assessed as having likely depression by usual clinical interview). In both conditions, nurses underwent 12-hour training course (3-hour lecture on postnatal depression and 9-hour workshop on non-directive counseling) in addition to basic professional and in-service training; also received ongoing support from doctors and community psychiatric team. Counseling lasted about 30-45 minutes, doctor not involved in study made final management recommendation according to protocol.	67 (29%) of IG women screened positive and thus should have received counseling, 16 did not; 4 of 9 additional cases identified through clinical assessment received counseling; overall, 55/76 (72.4%), or 23.8% of all IG group received counseling.	NR
MacArthur, 2002[34]	IG1	Care led by midwives w/referral to GP as needed. Systematic screening at 4-week postpartum, midwives trained in postpartum depression care. Symptom checklist at first visit, day 10 and 28, and at discharge (10-12 weeks); EPDS for depression screening at day 28 and discharge. Care plans made and visits scheduled based on sx and EPDS results. 10 evidence-based guidelines, summarized in leaflets, were used for subsequent midwife management of physical and psychological disorders. All midwives also trained in general postnatal care, health, and trial design. Continuing contact w/midwives included monthly visit from a study	Data recorded by midwives on the frequency of midwife home visits differed from that recorded by women (table 6). The duration of home visits was recorded only in the midwife records. On the basis of the	NR

Appendix E Table 2. Intervention Description of Depression Screening Studies (KQ1)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		midwife, daily telephone availability for consultations, and monthly newsletters.	number of midwife-recorded visits, the mean total midwife visit duration was 192.3 min (SD, 35.4) in the intervention; and based on the number of visits recorded by the women, mean duration was 186.9 (SD, 33.0).	
Morrell, 2009[35]	IG1	Health visitors trained (manualized) to identify depressive sx using EPDS (face-to-face and/or postal) and to use clinical assessment skills to assess mother's mood including suicidal thoughts; trained to deliver psychologically informed sessions based on CBT or person-centered principles. At-risk women (EPDS scores ≥12; found to be moderately to severely depressed via interview) asked to state their preference for psychological sessions, SSRI, or both. All other women offered usual care or psychological session if assessment indicates woman might benefit. EPDS assessments at 6 and 8 weeks postpartum, health visitor or GP informed if score ≥12.	NR	NR
Rost, 2001[36]	IG1	Physicians and nurses at intervention sites participated in a series of 4 1.5-hour conference calls. Calls reviewed study protocol, went over guidelines for detection and evaluation of depression in primary care, and provided training on pharmacological therapy and referral to mental health specialists. One nurse in each site also completed an 8-hour training session plus 1 phone call to: 1) review current clinical issues in detection and management of major depression in PC settings; 2) used manual and videotapes to train nurses in treatment protocol, and 3) use role playing and written test to ensure nurses mastery of material. Admin staff training in study protocol, including 2-stage depression screening. The objective of initial intervention was to increase the proportion of patients who received pharmacotherapy or psychotherapy for major depression. Once the intervention began, physicians in	Physicians and nurses in intervention sites participated in training calls. Nurses intervened with 92.5% of intervention patients and contacted them an average of 5.2 times during the study. 60% of contacts were by phone, 40% in-person.	NR

Appendix E Table 2. Intervention Description of Depression Screening Studies (KQ1)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		enhanced care practices were informed of their enrolled positive screening results, and told to evaluate the depression diagnosis, give the patient a copy of the AHCPR's Patient Guide to Depression, and ask the patient to return in 1 week to meet with the nurse and see the physician again. Immediately before this return visit, an office nurse trained to provide care management reassessed the patient's depressive symptoms, provided education about treatment options, asked the patient to complete "homework" assignments to increase his or her readiness to engage in active treatment, and arranged subsequent followup contacts. At the 1-week visit, the nurse assessed the 9 criteria for major depression, evaluated the patient's treatment preferences (drugs, CBT, watchful waiting) and identified barriers to care. Nurses provided physicians with a description of the patients' symptoms and treatment preferences for their review before seeing the patient on that same day. Phone and in-person followup took place for the next 5-8 weeks. Nurses prepared monthly patient summaries for providers. Long-term followup began at approximately 9 months after the initial visit. In telephone calls averaging 12 minutes in length, nurse care managers monitored depression symptoms, encouraged patients whose symptoms were resolving to adhere to treatment recommendations, and suggested to patients whose symptoms had not resolved that they raise this problem with their primary care doctor at their next visit. Patients reporting 3 or more of the 9 criteria for depression were called again the next month, whereas patients reporting fewer than 3 depression criteria were called again in 3 months. Primary care doctors reviewed monthly summaries of patient symptoms and current treatment prepared by nurse care managers, along with reminders to adjust treatment for symptomatic patients according to guidelines reviewed by psychiatrist.		
van der Weele, 2012[37]	IG1	PCPs instructed to inform screen-positive pts about their result and motivate them for referral to Community Mental Health Clinic for a stepped care intervention which included: 1) individual counseling about treatment needs and motivation of the patient during 1 or 2 home visits by a community psychiatric nurse; 2) coping with	101/121 screen positive pts in IG accepted referral to the community MHC to start the intervention.	NR

Appendix E Table 2. Intervention Description of Depression Screening Studies (KQ1)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		depression course; 3) referral back to GP to discuss further treatment if indicated. The Coping with Depression course was based on CBT and consists of 10 weekly group meetings with 2 course instructors and 6-10 participants. If patients could not attend, they were offered the course in-home.	Course participation was accepted by 23/101 (19%) and completed by 70%. 2 followed the course on individual basis, and 21 others participated in a group course. When adherence was examined by age group (75-79 v. 80+), similar rates of uptake with NS differences.	
van der Zee, 2017[38]	IG1	On initiation of the screening, a guideline was developed containing instructions on use of the EPDS, interpretation, and referral options. The guideline was discussed in structured, intercollegiate learning sessions by the professionals. During the home visit 2 weeks postpartum, the WCC nurse explained the purpose of screening for postpartum depression and asked the mother to complete an EPDS form before the WCC visits at 1, 3, and 6 months. During these visits, the WCC physician scored the EPDS and discussed the outcome with the mother. A score ≥13 was interpreted as indicating a high risk of having major depression. If the physician's clinical impression was consistent with the score, guideline instructions were to refer the mother to her family practitioner or mental health care professional. EPDS scores from 9 to 12 were an indication for minor depression. According to the guideline, mothers with scores from 9 to 12 were offered a home visit by the WCC nurse to clarify if the mothers could cope with these symptoms on their own, with support from WCC, or needed further referral. In case of suicidal ideation, 24-hour crisis services were available provided by the mental health care organizations in the region. Followup was part of standard care.	NR	NR
Wells, 2000[39]	IG1	QI-Med Support and QI-CBT groups analyzed together. In both IGs, practices provided in-kind resources; training provided to PCP, nursing supervisor, and MH specialist to implement the	NR	NR

Appendix E Table 2. Intervention Description of Depression Screening Studies (KQ1)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		interventions, including a 2-day workshop to review depression treatment and principals of collaborative care. Trained "leaders" distributed clinician manuals, initiated monthly lectures, and provided academic detailing prior to pt recruitment. Monthly team meetings held where leaders provided audit + feedback on the clinic or clinician level. Nurses also received 1-day workshop on how to conduct brief clinical assessments, patient education, and behavioral activation based on study manual/video. Monthly phone calls held between leaders and study team to review study progress. Other materials provided to sites (slides, pocket cards, videos, study charts, etc.). IG provided list of enrolled patients. In QI-Meds, nurse specialist performed initial patient assessment, PCP used that assessment to formulate a treatment plan with the patient. Nurses supported medication adherence through monthly visits or calls. QI-Meds patients able to access counseling via usual options with usual co-pay. In QI-Therapy, PCP used nurse assistant to formulate treatment plan with patient and referred, as appropriate, to CBT, available in English and Spanish. Study-trained psychotherapists provided individual and group CBT for a reduce co-pay ($0-10); patients could access other therapy for the usual co-payments ($20-35). Brief (4-session) CBT recommended for patients with minor depression. Medication treatment from regular PCP was available if preferred by patient, but nurse specialists did not provide monthly medication management followup.		
Wells, 2000[39]	IG2	In both IGs, practices provided in-kind resources; training provided to PCP, nursing supervisor, and MH specialist to implement the interventions, including a 2-day workshop to review depression treatment and principals of collaborative care. Trained "leaders" distributed clinician manuals, initiated monthly lectures, and provided academic detailing prior to pt recruitment. Monthly team meetings held where leaders provided audit + feedback on the clinic or clinician level. Nurses also received 1-day workshop on how to conduct brief clinical assessments, patient education, and behavioral activation based on study manual/video. Monthly phone calls held between leaders and study team to review study	NR	NR

Appendix E Table 2. Intervention Description of Depression Screening Studies (KQ1)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		progress. Other materials provided to sites (slides, pocket cards, videos, study charts, etc.). IG provided list of enrolled patients. In QI-Therapy, PCP used nurse assistant to formulate treatment plan with patient and referred, as appropriate, to CBT, available in English and Spanish. Study-trained psychotherapists provided individual and group CBT for a reduced co-pay ($0-10); patients could access other therapy for the usual co-payments ($20-35). Brief (4-session) CBT recommended for patients with minor depression. Medication treatment from regular PCP was available if preferred by patient, but nurse specialists did not provide monthly medication management followup.		
Wells, 2000[39]	IG3	In both IGs, practices provided in-kind resources; training provided to PCP, nursing supervisor, and MH specialist to implement the interventions, including a 2-day workshop to review depression treatment and principals of collaborative care. Trained "leaders" distributed clinician manuals, initiated monthly lectures, and provided academic detailing prior to pt recruitment. Monthly team meetings held where leaders provided audit + feedback on the clinic or clinician level. Nurses also received 1-day workshop on how to conduct brief clinical assessments, patient education, and behavioral activation based on study manual/video. Monthly phone calls held between leaders and study team to review study progress. Other materials provided to sites (slides, pocket cards, videos, study charts, etc.). IG provided list of enrolled patients. In QI-Meds, nurse specialist performed initial patient assessment, PCP used that assessment to formulate a treatment plan with the patient. Nurses supported medication adherence through monthly visits or calls. QI-Meds patients able to access counseling via usual options with usual co-pay.	NR	NR
Whooley, 2000[40]	IG1	Primary care physicians in the intervention clinics were notified of each participant's GDS score on the day of the participant's visit to the medical clinic and given an instruction sheet indicating the ranges of scores associated with depression. It was suggested that physicians refer participants with severe depressive symptoms (GDS ≥11) to the Psychiatry Department, and evaluate and treat participants with mild to moderate depressive symptoms (GDS	12% of participants attend the group sessions	NR

Appendix E Table 2. Intervention Description of Depression Screening Studies (KQ1)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		scores of 6–10) themselves. In addition, intervention clinic participants with depression were offered a series of organized educational group sessions on coping with depression. Family members were invited to attend the group sessions. This series, which consisted of 6 weekly educational sessions followed by 1 booster session 4 to 6 months later, was developed by a psychiatrist and led by a psychiatric nurse. Topics included the nature of depression, its clinical course, physical and emotional manifestations, relation to other medical conditions, treatment alternatives, medications and their side effects, coping mechanisms, and preventive strategies. Sessions were conducted at the Kaiser Permanente Medical Center Psychiatry Clinic. Study provided 1-hr educational sessions for clinicians at both IG and CG clinics on assessment of depression, differential diagnosis, suicidal risk assessment, management of depression, treatment options, duration of treatment, and evaluation of dementia vs. pseudo-dementia, which was attended by ~60% of clinicians.		
Wickberg, 2005[41]	IG1	Midwives received information about aim of study; also received a 1-afternoon session about different aspects of depression (e.g., sx, etiology, and effects) and about the value of listening and support. All women took EPDS at gestational week 25 and week 36; those who scored 12 at week 25 were phoned to ask for permission to disclose score to midwife.	NR	NR
Williams, 1999[42]	IG1	Combination of case-finding interventions (single question and 20-item CES-D instrument).	NR	Physician rating of case-finding helpfulness: 38% very helpful, 29% somewhat helpful, 29% no impact, 2% somewhat unhelpful, 2% very unhelpful. Staff physicians generally rated helpfulness higher than residents
Williams, 1999[42]	IG2	CES-D validated questionnaire w/20 items that focuses on	NR	NR

Appendix E Table 2. Intervention Description of Depression Screening Studies (KQ1)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		depressive symptoms in the last week; scores ≥16 identify people w/probable depression; self-administered unless pt could not read or requested it be read to them. All physicians given copy of "Quick Reference Guide for Clinicians" on managing depression in primary care and attended a continuing education session on interpreting case-finding questionnaires, diagnosing depression, and depression treatment.		
Williams, 1999[42]	IG3	Single question: "Have you felt depressed or sad much of the time in the past year?"; self-administered unless pt could not read or requested it be read to them. All physicians given copy of "Quick Reference Guide for Clinicians" on managing depression in primary care and attended a continuing education session on interpreting case-finding questionnaires, diagnosing depression, and depression treatment.	NR	NR
Yawn, 2012[43]	IG1	All women screened w/EPDS and PHQ-9 and queried about suicidal ideation; clinicians had routine access to screening test results. Clinicians were trained in a multistep postpartum depression screening and diagnosis process, practices provided w/a set of tools to facilitate diagnosis, followup, and postpartum depression management. The tools included an outline for the content of followup postpartum depression visits, including repeated use of the PHQ-9 to help determine response to therapy, and a written format for nursing followup telephone calls that dealt with medication initiation, adherence, and side effects. Selection, modification, and followup of specific types of therapy were left to the discretion of the physician and patient, with the support tools to describe common side effects and usual dose range for medications and an explanation of cognitive behavioral therapy. Standard recommended was for 6 in-person contacts and 5 to 9 nurse calls (number depending on the duration of symptoms) to monitor symptoms and support treatment engagement. Materials also included an immediate action protocol for patients at high risk of suicide.	250/287 (87%) of IG diagnosed w/depression received ≥1 nursing support calls; 5 had no attempted contacts. Only 22% had ≥2 calls (mean, 2.3 calls). No women in CG had a followup call. Loss of insurance potential reason for lack of followup calls.	NR

Abbreviations: AHRQ = Agency for Healthcare Research and Quality; CBT = cognitive behavioral therapy; CES-D = Center for Epidemiological Studies Depression; EPDS = Edinburgh Postnatal Depression Scale; GDS = Geriatric Depression Scale; GP = general practitioner; IG = intervention group; MHC = mental health care; NR = not reported; PC = primary care; PCP = primary care provider; PHN = public health nurse; PHQ = Patient Health Questionnaire; PPD =

postpartum depression; PRIME-MD = Primary Care Evaluation of Mental Disorders; QI = quality improvement; SSRIs = selective serotonin reuptake inhibitors; WCC = well-child care.

Appendix E Table 3. Depression Prevalence Results for Studies of Depression Screening (KQ1)

Author (Pop)	Measure	IG	Analyzed	FUP, wks	OR (95% CI)	IG n/N (%)	CG n/N (%)	p-value	Adj
Williams, 1999[42] (G)	Depression dx	IG1	All	13	0.67 (0.37 to 1.21)	56/153 (37.0)	30/65 (46.0)	0.19	Yes
Glavin, 2010[30] (PP)	EPDS ≥ 10	IG1	All	p13	0.4 (0.3 to 0.6)	65/1516 (4.3)	42/405 (10.4)	<0.05	No
	EPDS ≥ 10	IG1	All	p26 (20)	0.5 (0.3 to 0.8)	40/1122 (3.6)	32/367 (8.8)	<0.05	No
	EPDS ≥ 10	IG1	All	0	0.6 (0.4 to 0.8)	164/1806 (9.1)	64/441 (14.5)	<0.05	No
Leung, 2011[33] (PP)	EPDS ≥ 10	IG1	All	p26 (18)	0.53 (0.32 to 0.86)	30/231 (13.0)	51/231 (22.1)	<0.05	No
	EPDS ≥ 10	IG1	All	p78	1.11 (0.66 to 1.88)	34/231 (14.7)	31/231 (13.4)	NR, NSD	NR
Morrell, 2009[35] (PP)	EPDS ≥12	IG1	All	p26 (20)	0.67 (0.52 to 0.86)	205/1745 (11.7)	150/914 (16.4)	0.002	Yes
	EPDS ≥12	IG1	All	0	1.11 (0.92 to 1.34)	404/2277 (17.7)	191/1172 (16.3)	NR	NR
Wickberg, 2005[41] (Pr)	EPDS ≥12	IG1	All	g36 (11)	0.8 (0.48 to 1.35)	26/273 (9.5)	40/345 (11.5)	<0.001	NR
	EPDS ≥12	IG1	All	0	1.21 (0.78 to 1.87)	48/318 (15.1)	45/351 (12.8)	NR	NR
MacArthur, 2002[34] (PP)	EPDS ≥13	IG1	All	p17 (12)	0.47 (0.31 to 0.76)	115/801 (14.4)	149/702 (21.2)	<0.05	Yes
Whooley, 2000[40] (O)	GDS ≥6	IG1	GDS ≥11 at BL	104	0.8 (0.2 to 3.4)	8/13 (62.0)	14/21 (67.0)	0.8	No
	GDS ≥6	IG1	All	104	0.7 (0.4 to 1.3)	41/97 (42.0)	54/109 (50.0)	0.3	No
van der Zee, 2017[38] (PP)	Major and minor depression diagnosis	IG1	All	p39 (36)	0.38 (0.24 to 0.61)	56/1843 (3.0)	105/1246 (8.4)	<0.001	Yes
	Major depression diagnosis	IG1	All	p39 (36)	0.3 (0.13 to 0.66)	11/1843 (0.6)	31/1246 (2.5)	0.001	Yes

Abbreviations: Adj = adjusted; BL = baseline; CG = control group; dx = diagnosis; EPDS = Edinburgh Postnatal Depression Scale; FUP = followup; G = general adults; GDS = Geriatric Depression Scale; IG = intervention group; NR = not reported; NSD = no significant difference; O = older adults; OR = odds ration; Pop = population; PP = postpartum population; Pr = pregnant population; wks = weeks.

Appendix E Table 4. Depression Remission Results for Studies of Depression Screening (KQ1)

Author, Year (Pop)	Measure	IG	Analyzed	FUP, wks	OR (95% CI)	IG n/N (%)	CG n/N (%)	p-value	Adj
Williams, 1999[42] (G)	≤1 MDD sx	IG1	Depression dx at BL	13	2.51 (0.98 to 6.44)	32/67 (48.0)	8/30 (27.0)	<0.05	Yes
Rost, 2001[36] (G)	CESD <16	IG1	New treatment episode	26	1.51 (0.79 to 2.9)	30/97 (31.0)	21/92 (23.0)	NR	NR
	CESD <16	IG1	New treatment episode	52	2.33 (1.24 to 4.4)	40/85 (47.0)	24/87 (28.0)	NR	NR
	CESD <16	IG1	New treatment episode	104	4.06 (1.99 to 8.27)	51/69 (74.0)	30/73 (41.0)	<0.05	No
Wells, 2000[39] (G)	CESD <20	IG1	All	26	1.46 (1.13 to 1.88)	343/770 (44.6)	137/386 (35.6)	0.005	Yes
	CESD <20	IG1	All	52	1.33 (1.03 to 1.72)	342/752 (45.5)	144/374 (38.6)	0.04	Yes
	CIDI negative, full	IG2	All	104	1.14 (0.85 to 1.54)	285/413 (69.0)	255/386 (66.0)	NSD	Yes
	CIDI negative, full	IG3	All	104	0.81 (0.6 to 1.09)	218/357 (61.0)	255/386 (66.0)	NSD	Yes
	CIDI negative, 2-item	IG1	All	26	1.51 (1.18 to 1.93)	463/770 (60.1)	193/386 (50.1)	0.001	Yes
	CIDI negative, 2-item	IG1	All	52	1.46 (1.14 to 1.88)	439/752 (58.4)	183/374 (48.8)	0.005	Yes
	CIDI negative, 2-item	IG1	All	104	1.03 (0.81 to 1.31)	482/835 (57.7)	235/413 (57.0)	NR	NR
	CIDI negative, 2-item	IG1	Black or Latinx	260	1.89 (1.18 to 3.04)	133/220 (60.5)	46/103 (44.2)	NR	NR
	CIDI negative, 2-item	IG1	All	260	1.32 (1 to 1.73)	428/679 (63.0)	176/312 (56.4)	NR	NR
	CIDI negative, 2-item	IG1	White	260	1.13 (0.8 to 1.62)	274/410 (66.8)	128/200 (64.0)	NR	NR
	CIDI negative, 2-	IG2	All	26	1.5 (1.15 to 1.97)	263/446 (59.0)	202/413 (49.0)	<0.05	Yes

Appendix E Table 4. Depression Remission Results for Studies of Depression Screening (KQ1)

Author, Year (Pop)	Measure	IG	Analyzed	FUP, wks	OR (95% CI)	IG n/N (%)	CG n/N (%)	p-value	Adj
	item								
	CIDI negative, 2-item	IG2	All	52	1.32 (1.01 to 1.73)	263/446 (59.0)	215/413 (52.0)	<0.05	Yes
Wells, 2000[39] continued (G)	CIDI negative, 2-item	IG2	All	104	1.14 (0.87 to 1.5)	268/446 (60.0)	235/413 (57.0)	NSD	Yes
	CIDI negative, 2-item	IG2	All	260	1.37 (1 to 1.86)	228/357 (63.8)	176/312 (56.4)	0.05	Yes
	CIDI negative, 2-item	IG2	Black or Latinx	260	2.26 (1.33 to 3.84)	84/130 (64.4)	46/103 (44.2)	0.01	Yes
	CIDI negative, 2-item	IG2	White	260	0.93 (0.61 to 1.42)	131/200 (65.6)	128/191 (64.0)	0.74	Yes
	CIDI negative, 2-item	IG3	All	26	1.51 (1.14 to 2)	230/389 (59.0)	202/413 (49.0)	<0.05	Yes
	CIDI negative, 2-item	IG3	All	52	1.28 (0.97 to 1.69)	226/389 (58.0)	215/413 (52.0)	<0.05	Yes
	CIDI negative, 2-item	IG3	All	104	0.93 (0.7 to 1.22)	214/389 (55.0)	235/413 (57.0)	NSD	Yes
	CIDI negative, 2-item	IG3	White	260	1.2 (0.8 to 1.81)	143/210 (68.1)	128/200 (64.0)	0.34	Yes
	CIDI negative, 2-item	IG3	All	260	1.27 (0.92 to 1.74)	200/322 (62.1)	176/312 (56.4)	0.08	Yes
	CIDI negative, 2-item	IG3	Black or Latinx	260	1.48 (0.84 to 2.61)	49/90 (54.6)	46/103 (44.2)	0.13	Yes
Glavin, 2010[30] (PP)	EPDS <10	IG1	EPDS ≥10 at BL	p13	2.34 (1.22 to 4.49)	95/128 (74.2)	32/58 (55.2)	NR	NR
	EPDS <10	IG1	EPDS ≥10 at BL	p26 (20)	2.34 (1.1 to 4.97)	75/96 (78.1)	29/48 (60.4)	NR	NR

Appendix E Table 4. Depression Remission Results for Studies of Depression Screening (KQ1)

Author, Year (Pop)	Measure	IG	Analyzed	FUP, wks	OR (95% CI)	IG n/N (%)	CG n/N (%)	p-value	Adj
Morrell, 2009[35] (PP)	EPDS<12	IG1	EPDS ≥12 at p06	p26 (20)	1.67 (1.05 to 2.63)	179/271 (66.1)	80/147 (54.4)	0.028	Yes
Wickberg, 2005[41] (Pr)	EPDS<12	IG1	EPDS ≥12 at BL	g36 (11)	4.81 (1.81 to 12.8)	22/42 (52.4)	8/43 (18.6)	NR	NR
Callahan, 1994[29] (O)	HAM-D≤10	IG1	All	26	1.06 (0.34 to 3.28)	10/76 (13.2)	7/60 (11.7)	NR	No
Bijl, 2003[28] (O)	MADRS <10	IG1	All	8	1.33 (0.61 to 2.89)	18/67 (27.0)	16/74 (22.0)	NR, NSD	Yes
	MADRS <10	IG1	All	26	2.49 (1.19 to 5.24)	29/60 (48.0)	18/66 (66.0)	<0.05	Yes
	MADRS <10	IG1	All	52	1.14 (0.56 to 2.32)	26/56 (46.0)	29/67 (43.0)	NR, NSD	Yes
Bergus, 2005[27] (G)	PHQ-9 <5	IG1	PHQ-9 ≥10 at BL	10	0.93 (0.21 to 4.11)	5/14 (36.0)	6/16 (38.0)	NR, NSD	No
	PHQ-9 <5	IG1	All	10	2.01 (0.66 to 6.16)	13/24 (54.0)	10/27 (37.0)	0.22	No
	PHQ-9 <5	IG1	All	24	1.7 (0.56 to 5.2)	12/24 (52.0)	10/27 (38.0)	0.35	No
	PHQ-9 <5	IG1	PHQ-9 ≥10 at BL	24	2.93 (0.66 to 13.09)	8/14 (54.0)	5/16 (31.0)	NR, NSD	No
Bijl, 2003[28] (O)	PRIME-MD recovered	IG1	All	26	0.89 (0.43 to 1.85)	35/58 (60.3)	41/65 (63.1)	NR, NSD	No
	PRIME-MD recovered	IG1	All	52	0.83 (0.41 to 1.68)	25/58 (43.1)	32/67 (47.8)	0.60	No

Abbreviations: Adj = adjusted; BL = baseline; CES-D = Center for Epidemiological Studies Depression; CG = control group; CIDI = Composite International Diagnostic Interview; dx = diagnosis; EPDS = Edinburgh Postnatal Depression Scale; FUP = followup; g = weeks' gestation; G = general adults; GDS = Geriatric Depression Scale; IG = intervention group; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; NR = not reported; NSD = no significant difference; O = older adults; OR = odds ratio; p = weeks postpartum; PHQ = Patient Health Questionnaire; Pop = population; PP = postpartum population; PRIME-MD = Primary Care Evaluation of Mental Disorders; wks = weeks.

Appendix E Table 5. Depression Response Results for Studies of Depression Screening (KQ1)

Author, Year (Pop)	Measure	IG	Analyzed	FUP, wks	OR (95% CI)	IG n/N (%)	CG n/N (%)	p-value	Adj
Jarjoura, 2004[31] (G)	10-pt reduction in BDI-II	IG1	All	52	2.3 (0.69 to 7.7)	11/33 (32.0)	5/28 (17.0)	NR	NR
Bijl, 2003[28] (O)	50% decrease in MADRS	IG1	All	8	2.36 (1.05 to 5.28)	21/67 (31.0)	12/74 (16.0)	<0.05	Yes
	50% decrease in MADRS	IG1	All	26	2.06 (0.97 to 4.37)	25/60 (42.0)	17/66 (26.0)	NR, NSD	Yes
	50% decrease in MADRS	IG1	All	52	1.37 (0.67 to 2.81)	26/56 (46.0)	26/67 (39.0)	NR, NSD	Yes
van der Weele, 2012[37] (O)	50% decrease in MADRS	IG1	Age 75-79	26	0.8 (0.27 to 2.35)	7/47 (14.9)	9/50 (18.0)	0.68	No
	50% decrease in MADRS	IG1	All	26	0.66 (0.33 to 1.32)	17/107 (15.9)	23/103 (22.3)	0.24	No
	50% decrease in MADRS	IG1	Age 80+	26	0.56 (0.22 to 1.39)	10/60 (16.7)	14/53 (26.4)	0.21	No
	50% decrease in MADRS	IG1	All	52	0.52 (0.28 to 1)	21/101 (20.8)	31/93 (33.3)	0.049	No
	50% decrease in MADRS	IG1	Age 75-79	52	0.51 (0.22 to 1.22)	13/46 (28.3)	20/46 (43.5)	0.13	No
	50% decrease in MADRS	IG1	Age 80+	52	0.56 (0.2 to 1.53)	8/55 (14.5)	11/47 (23.4)	0.25	No
Bergus, 2005[27] (G)	50% decrease in PHQ-9	IG1	PHQ-9 ≥10 at BL	10	1.08 (0.24 to 4.79)	9/14 (64.0)	10/16 (60.0)	NR, NSD	No
	50% decrease in PHQ-9	IG1	All	10	2.15 (0.69 to 6.71)	16/24 (67.0)	13/27 (48.0)	NR, NSD	No
	50% decrease in PHQ-9	IG1	All	24	1.08 (0.36 to 3.24)	12/24 (52.0)	13/27 (48.0)	NR, NSD	No
	50% decrease in PHQ-9	IG1	PHQ-9 ≥10 at BL	24	1.94 (0.42 to 8.92)	10/14 (69.0)	9/16 (54.0)	NR, NSD	No
Yawn, 2012[43] (PP)	5-pt decrease in PHQ-9	IG1	EPDS ≥10 at BL	p52 (44)	1.74 (1.05 to 2.86)	98/219 (45.0)	60/178 (35.0)	NR	Yes

Abbreviations: Adj = adjusted; BL = baseline; BDI = Beck Depression Inventory; CG = control group; dx = diagnosis; FUP = followup; g = weeks' gestation; G = general adults; IG = intervention group; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; NR = not reported; NSD = no significant difference; O = older adults; OR = odds ratio; p = weeks postpartum; Pop = population; PP = perinatal population; PHQ = patient health questionnaire; wks = weeks.

Appendix E Table 6. Depression Symptom Severity Results for Studies of Depression Screening (KQ1)

Author, year (Pop)	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Bergus, 2005[27] (G)	PHQ-9	0-27	Worse	All	IG1	10	24	27	12 (NR)	12.7 (NR)	-5.8 (NR)	-5.8 (NR)	NR	NR, NSD	Yes
	PHQ-9	0-27	Worse	All	IG1	24	24	27	12 (NR)	12.7 (NR)	-5.7 (NR)	-5 (NR)	NR	0.45	Yes
	PHQ-9	0-27	Worse	PHQ-9 ≥10 at BL	IG1	10	14	16	16.1 (NR)	15.4 (NR)	-7.3 (NR)	-9.1 (NR)	NR	NR, NSD	Yes
	PHQ-9	0-27	Worse	PHQ-9 ≥10 at BL	IG1	24	14	16	16.1 (NR)	15.4 (NR)	-8.5 (NR)	-8.2 (NR)	NR	NR, NSD	Yes
Jarjoura, 2004[31] (G)	BDI-II	0-63	Worse	All	IG1	26	28	33	28 (10.6)	23 (11.5)	NR	NR	-7.6 (-15 to -0.4)	NR	No
	BDI-II	0-63	Worse	All	IG1	52	28	33	28 (10.6)	23 (11.5)	NR	NR	-6.5 (-14 to 1.2)	NR	No
Kroenke, 2018[32] (G)	PROMIS-Depression	4-20	Worse	All	IG1	13	151	149	55.8 (10.4)	56 (9.1)	-3.1 (NR)	-1.6 (NR)	-1.5 (NR)	0.174	NR
Rost, 2001[36] (G)	CESD	0-60	Worse	In treatment at BL	IG1	26	NR	NR	56.9 ()	57.4 ()	-14.5 (NR)	-11 (NR)	-3.5 (NR)	NR, NSD	Yes
	CESD	0-60	Worse	New treatment episode	IG1	26	97	92	55.1 (NR)	52.7 (NR)	-21.7 (NR)	-13.7 (NR)	-8.2 (-0.2 to -16.1)	0.04	Yes
Bijl, 2003[28] (O)	GDS	0-15	Worse	All	IG1	8	70	75	7.3 (NR)	7.6 (NR)	-1.8 (NR)	-1.8 (NR)	NR	NR, NSD	Yes
	PRIME-MD	NR	Worse	All	IG1	26	70	75	6.1 (6.7)	6.3 (8.7)	-3.3 (7.9)	-2.3 (9.8)	-1 (-3.9 to 1.9)	NR, NSD	Yes
	GDS	0-15	Worse	All	IG1	26	70	75	7.3 (NR)	7.6 (NR)	-2.6 (NR)	-2.4 (NR)	NR	NR, NSD	Yes
	MADRS	0-60	Worse	All	IG1	52	58	67	19.3 (8.7)	18.7 (7.7)	-7.8 (9)	-7.2 (9)	-0.6 (-3.8 to	0.70	Yes

Appendix E Table 6. Depression Symptom Severity Results for Studies of Depression Screening (KQ1)

Author, year (Pop)	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
													2.6)		
	PRIME-MD	NR	Worse	All	IG1	52	70	75	6.1 (6.7)	6.3 (8.7)	-2.9 (7.9)	-2.6 (9.7)	-0.3 (-3.2 to 2.6)	NR, NSD	Yes
	GDS	0-15	Worse	All	IG1	52	70	75	7.3 (NR)	7.6 ()	-2.6 (NR)	-2.9 (NR)	NR	NR, NSD	Yes
Callahan, 1994[29] (O)	HAM-D	0-52	Worse	All	IG1	26	76	60	22 (NR)	21.8 (NR)	-4.2 (NR)	-4.9 (NR)	NR	NR, NSD	No
	HAM-D	0-52	Worse	All	IG1	39	NR	NR	22 (NR)	21.8 (NR)	-6.1 (NR)	-7 (NR)	NR	NR, NSD	No
van der Weele, 2012[37] (O)	MADRS	0-60	Worse	Age 75-79	IG1	26	47	50	NR	NR	-1.2 (6.5)	-3 (5.7)	1.6 (-0.6 to 4.2)	0.12	Yes
	MADRS	0-60	Worse	Age 75-79	IG1	52	46	46	NR	NR	-4.3 (6.2)	-4.6 (5.2)	0.3 (-2 to 2.6)	0.36	Yes
	MADRS	0-60	Worse	Age 80+	IG1	26	60	53	NR	NR	-0.9 (6.2)	-2.7 (6.1)	1.2 (-0.5 to 4.1)	0.25	Yes
	MADRS	0-60	Worse	Age 80+	IG1	52	55	47	NR	NR	-2 (6)	-4.6 (7.1)	2.6 (0.1 to 5.1)	0.12	Yes
	MADRS	0-60	Worse	All	IG1	26	107	103	NR	NR	-1.1 (6.3)	-2.9 (5.9)	1.4 (0.1 to 3.5)	0.056	Yes
	MADRS	0-60	Worse	All	IG1	52	101	93	NR	NR	-3.1 (6.1)	-4.6 (6.2)	1.5 (-0.2 to 3.2)	0.0888	Yes

Appendix E Table 6. Depression Symptom Severity Results for Studies of Depression Screening (KQ1)

Author, year (Pop)	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Whooley, 2000[40] (O)	GDS	0-15	Worse	All	IG1	104	76	97	8.2 (26.7)	8.4 (31.2)	-1.8 (3.5)	-2.2 (3.9)	0.3 (-0.7 to 1.4)	0.41	Yes
	GDS	0-15	Worse	GDS ≥11 at BL	IG1	104	13	21	NR	NR	-5.6 (4.3)	-3.4 (4.1)	-2.2 (-5.1 to 0.7)	0.15	Yes
	GDS	0-15	Worse	GDS 6-10 at BL	IG1	104	69	76	NR	NR	-1.6 (3.3)	-1.8 (3.5)	0.2 (-0.9 to 1.3)	0.70	Yes
Glavin, 2010[30] (PP)	EPDS	0-30	Worse	All	IG1	p13	1516	405	NR	NR	FU=3.8 (3.4)	FU=4.9 (3.8)	NR	NR	NR
	EPDS	0-30	Worse	All	IG1	p26 (20)	1122	367	NR	NR	FU=3.1 (3.3)	FU=4.8 (3.3)	NR	NR	NR
	EPDS	0-30	Worse	EPDS ≥10 at BL	IG1	p13	128	58	12.6 (3.6)	12.5 (2.4)	-5.4 (4.9)	-2.7 (4.7)	-2.7 (-4.2 to -1.2)	0.001	No
	EPDS	0-30	Worse	EPDS ≥10 at BL	IG1	p26 (20)	97	49	12.6 (3.6)	12.5 (2.4)	-5.9 (4.9)	-3.4 (4.8)	-2.5 (-4.2 to -0.8)	0.003	No
Leung, 2011[33] (PP)	EPDS	0-30	Worse	All	IG1	p26 (18)	231	231	6.4 (4.3)	NR	-1.3 (3.8)	FU=6.5 (4.4)	NR	<0.001	No
	EPDS	0-30	Worse	All	IG1	p78	231	231	6.4 (4.3)	NR	-0.7 (3.9)	FU=5.8 (3.6)	NR	0.819	No
MacArthur, 2002[34] (PP)	EPDS	0-30	Worse	All	IG1	p17 (12)	801	702	()	NR	FU=6.4 (0.4)	FU=8.1 (11.1)	-1.7 (-2.5 to -0.8)	<0.0001	No
Morrell, 2009[35] (PP)	EPDS	0-30	Worse	All	IG1	p26 (20)	1745	914	6.6 (4.8)	6.8 (5)	-1.1 (4.8)	-0.4 (5.1)	-1 (-1.5 to -0.4)	0.001	Yes

Appendix E Table 6. Depression Symptom Severity Results for Studies of Depression Screening (KQ1)

Author, year (Pop)	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
	EPDS	0-30	Worse	EPDS ≥12 at p06	IG1	p26 (20)	271	147	15.1 (2.9)	15.4 (3.2)	-5.9 (4.7)	-4.1 (5)	-2.1 (-3.4 to -0.8)	0.002	Yes
Wickberg, 2005[41] (Pr)	EPDS	0-30	Worse	All	IG1	g36 (11)	226	231	6.4 (6.2)	6.1 (5.2)	-1 (5.7)	0 (5.4)	-1.1 (-2.1 to 0)	<0.05	NR

Abbreviations: Adj = adjusted; BL = baseline; BDI = Beck Depression Inventory; CES-D = Center for Epidemiological Studies Depression; CG = control group; CI = confidence interval; Diff = difference; dx = diagnosis; EPDS = Edinburgh Postnatal Depression Scale; FUP = followup; g = weeks' gestation; G = general adults; GDS = Geriatric Depression Scale; HAM-D = Hamilton Rating Scale for Depression; IG = intervention group; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; NR = not reported; NSD = no significant difference; O = older adults; p = weeks postpartum; PHQ = Patient Health Questionnaire; Pop = population; PP = postpartum population; Pr = pregnant population; PRIME-MD = Primary Care Evaluation of Mental Disorders; PROMIS = Patient Reported Outcomes Measurement Information System; SD = standard deviation; wks = weeks.

Appendix E Table 7. Other Continuous Measures of Mental Health Results for Studies of Depression Screening (K1)

Author, Year (Pop)	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Kroenke, 2018[32] (G)	Anxiety symptoms	PROMIS-Anxiety	4-20	Worse	All	IG1	13	151	149	59 (10.1)	59.2 (8.7)	-3 (NR)	-2.1 (NR)	-0.8 (NR)	0.471	NR
Morrell, 2009[35] (PP)	Anxiety symptoms	STAI	20-80	Worse	All	IG1	p26 (20)	1634	858	NR	NR	FU=33.2 (10.9)	FU=34.3 (11.7)	-1.3 (-2.7 to -0.1)	0.042	Yes
	Anxiety symptoms	STAI	20-80	Worse	EPDS ≥12 at p06	IG1	p26 (20)	254	136	NR	NR	FU=41.7 (11.8)	FU=45.5 (12.5)	-3.8 (-6.6 to 1)	0.008	Yes
van der Zee, 2017[38] (PP)	Anxiety symptoms	STAI-6	NR	Worse	All	IG1	p52	1843	1246	NR	NR	FU=33.9 (NR)	FU=37.3 (NR)	-3.1 (-4.4 to -1.8)	<0.001	Yes
Morrell, 2009[35] (PP)	Other suicide-related	CORE-OM self-harm risk	NR	Worse	All	IG1	p26 (20)	1736	906	NR	NR	FU=0 (0.2)	FU=0.1 (0.2)	0 (0 to 0)	0.143	Yes
	Other suicide-related	CORE-OM self-harm risk	NR	Worse	EPDS ≥12 at p06	IG1	p26 (20)	269	145	NR	NR	FU=0.1 (0.2)	FU=0.2 (0.4)	0 (-0.1 to 0)	0.149	Yes
Leung, 2011[33] (PP)	Global mental health symptoms	GHQ	0-100	Worse	All	IG1	p26 (18)	231	231	NR	NR	FU=1.1 (0.8)	FU=1.4 (2.2)	NR	0.084	No
	Global mental health symptoms	GHQ	0-100	Worse	All	IG1	p78	231	231	NR	NR	FU=1.8 (2.6)	FU=1.8 (3.1)	NR	0.727	No
Morrell, 2009[35] (PP)	Global mental health symptoms	CORE-OM well-being	NR	Worse	All	IG1	p26 (20)	1735	907	NR	NR	FU=0.7 (0.7)	FU=0.8 (0.8)	-0.1 (-0.1 to 0)	0.015	Yes
	Global mental health symptoms	CORE-OM	0-40	Worse	All	IG1	p26 (20)	1736	906	0.5 (0.5)	0.6 (0.5)	-0.1 (0.5)	0 (0.5)	-0.1 (-0.2 to 0)	0.001	Yes
	Global	CORE-	0-40	Worse	EPDS	IG1	p26	269	146	1.4	1.4	7.8 (5.2)	9.9 (5.6)	-2.3	0.006	Yes

Appendix E Table 7. Other Continuous Measures of Mental Health Results for Studies of Depression Screening (K1)

Author, Year (Pop)	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
	mental health symptoms	OM			≥12 at p06		(20)			(0.5)	(0.5)			(-0.4 to -0.1)		
	Global mental health symptoms	CORE-OM well-being	NR	Worse	EPDS ≥12 at p06	IG1	p26 (20)	269	146	NR	NR	FU=1.2 (0.9)	FU=1.6 (0.9)	-0.3 (-0.5 to -0.2)	0.001	Yes

Abbreviations: Adj = adjusted; BL = baseline; CG = control group; CI = confidence interval; CORE-OM = Clinical Outcomes Routine Evaluation – Outcome Measure; Diff = difference; dx = diagnosis; FUP = followup; g = weeks' gestation; G = general adults; IG = intervention group; NR = not reported; O = older adults; p = weeks postpartum; Pop = population; PP = postpartum population; Pr = pregnant population; PROMIS = Patient Reported Outcomes Measurement Information System; SD = standard deviation; STAI = Spielberger State-Trait Anxiety Inventory; wks = weeks.

Appendix E Table 8. Quality of Life and Functioning Outcomes for Studies of Depression Screening (KQ1)

Author, Year (Pop)	Measure	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Jarjoura, 2004[31] (G)	SF-36 Total	Better	All	IG1	52	33	28	NR	NR	NR	NR	3.6 (-2.8 to 10)	0.27	Yes
Rost, 2001[36] (G)	SF-36 PCS	Better	New treatment episode	IG1	24	97	92	50 (NR)	50 (NR)	6 (NR)	1 (NR)	NR	NR	Yes
	SF-36 MCS	Better	New treatment episode	IG1	26	97	92	35 (NR)	35 (NR)	30 (NR)	23 (NR)	NR	NR	Yes
	SF-36 MCS	Better	New treatment episode	IG1	52	85	87	35 (NR)	35 (NR)	34 (NR)	22 (NR)	NR	NR	Yes
	SF-36 PCS	Better	New treatment episode	IG1	52	85	87	50 (NR)	50 (NR)	10 (NR)	1 (NR)	NR	NR	Yes
	SF-36 MCS	Better	New treatment episode	IG1	104	69	73	35 (NR)	35 (NR)	38 (NR)	14 (NR)	NR	0.002	Yes
	SF-36 PCS	Better	New treatment episode	IG1	104	69	73	50 (NR)	50 (NR)	13 (NR)	-4 (NR)	NR	0.005	Yes
Wells, 2000[39] (G)	SF-12 MCS	Better	All	IG1	26	770	386	35.6 (12.4)	36.1 (10.9)	6 (12.7)	3.7 (11.1)	2.3 (0.8 to 3.8)	0.009	Yes
	SF-12 PCS	Better	All	IG1	26	770	386	45.2 (12.4)	44.6 (11.2)	-1.3 (12.4)	-0.9 (10.7)	-0.4 (-1.9 to 1.1)	0.72	Yes
	SF-12 MCS	Better	All	IG1	52	752	374	35.6 (12.4)	36.1 (10.9)	5.3 (12.8)	3.2 (11.5)	2.1 (0.6 to 3.6)	0.04	Yes
	SF-12 PCS	Better	All	IG1	52	752	374	45.2 (12.	44.6 (11.2)	-1.1 (12.1)	0 (10.5)	-1.1 (-2.5	0.38	Yes

Appendix E Table 8. Quality of Life and Functioning Outcomes for Studies of Depression Screening (KQ1)

Author, Year (Pop)	Measure	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
								NR 4)				to 0.3)		
Wells, 2000[39] continued (G)	SF-12 MCS	Better	All	IG2	26	464	386	34.9 (10.4)	36.4 (11)	7 (NR)	3.4 (11.1)	NR	<0.05	Yes
	SF-12 MCS	Better	All	IG2	52	464	374	34.9 (10.4)	36.4 (11)	7.3 (NR)	2.9 (11.5)	NR	<0.05	Yes
	SF-12 MCS	Better	All	IG2	104	464	430	34.9 (10.4)	36.4 (11)	7.8 (NR)	4.2 ()	NR	<0.05	Yes
	SF-12 MCS	Better	All	IG2	260	357	312	34.9 (10.4)	36.4 (11)	9.4 (21.4)	6.2 (13.7)	3.2 (0.4 to 6)	0.14	Yes
	SF-12 MCS	Better	All	IG3	26	405	386	36 (10.8)	36.4 (11)	4.9 (NR)	3.4 (11.1)	NR	<0.05	Yes
	SF-12 MCS	Better	All	IG3	52	405	374	36 (10.8)	36.4 (11)	4.9 (NR)	2.9 (11.5)	NR	<0.05	Yes
	SF-12 MCS	Better	All	IG3	104	405	430	36 (10.8)	36.4 (11)	4.8 (NR)	4.2 (NR)	NR	NR, NSD	Yes
	SF-12 MCS	Better	All	IG3	260	322	312	36 (10.8)	36.4 (11)	7.9 (17.5)	6.2 (13.7)	1.7 (-0.7 to 4.1)	0.21	Yes
	SF-12 MCS	Better	Black or Latinx	IG2	260	130	103	NR	NR	FU=44.5 (30)	FU=40 (14.5)	NR	0.03	Yes
	SF-12 MCS	Better	Black or Latinx	IG3	260	90	103	NR	NR	FU=41.6 (16)	FU=40 (14.5)	NR	0.35	Yes
	SF-12 MCS	Better	White	IG2	260	200	191	NR	NR	FU=44.6 (12.3)	FU=44.5 (11.3)	NR	0.92	Yes
	SF-12 MCS	Better	White	IG3	260	210	191	NR	NR	FU=45.4 (16.3)	FU=44.5 (11.3)	NR	0.45	Yes
Bijl, 2003[28] (O)	SF-36 MCS	Better	All	IG1	8	70	75	47 (NR)	50.2 (NR)	7.4 (NR)	4.4 (NR)	NR	NR, NSD	Yes
	SF-36 PCS	Better	All	IG1	8	70	75	60.5 (NR)	61.2 (NR)	0.2 (NR)	2.3 (NR)	NR	NR, NSD	Yes
	SF-36 PCS	Better	All	IG1	26	70	75	60.5 (NR)	61.2 (NR)	0.9 (NR)	1.9 (NR)	NR	NR, NSD	Yes

Appendix E Table 8. Quality of Life and Functioning Outcomes for Studies of Depression Screening (KQ1)

Author, Year (Pop)	Measure	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Bijl, 2003[28] continued (O)	SF-36 MCS	Better	All	IG1	26	70	75	47 (NR)	50.2 (NR)	11.4 (NR)	7.4 (NR)	NR	NR, NSD	Yes
	EuroQoL	Better	All	IG1	26	70	75	62 (NR)	62.3 (NR)	2.9 (NR)	3.6 (NR)	NR	NR, NSD	Yes
	EuroQoL	Better	All	IG1	52	70	75	62 (NR)	62.3 (NR)	0.4 (NR)	0.6 (NR)	NR	NR, NSD	Yes
	SF-36 MCS	Better	All	IG1	52	70	75	47 (NR)	50.2 (NR)	12.2 (NR)	10.4 (NR)	NR	NR, NSD	Yes
	SF-36 PCS	Better	All	IG1	52	70	75	60.5 (NR)	61.2 (NR)	0.2 (NR)	2.4 (NR)	NR	NR, NSD	Yes
	QALYs gained	Better	All	IG1	52	58	67	NR	NR	0.6 (0.2)	0.7 (0.2)	-0.1 (-0.1 to 0)	0.20	No
van der Weele, 2012[37] (O)	QALYs gained	Better	Age 75-79	IG1	52	54	55	NR	NR	FU=0.6 (NR)	FU=0.6 (NR)	NR	0.78	NR
	QALYs gained	Better	Age 80+	IG1	52	54	55	NR	NR	FU=0.6 (NR)	FU=0.6 (NR)	NR	0.46	NR
MacArthur, 2002[34] (PP)	SF-36 PCS	Better	All	IG1	p17 (12)	801	702	NR	NR	FU=46.7 (12.8)	FU=47.8 (18.9)	-1.2 (-2.5 to 0.2)	0.089	No
	SF-36 MCS	Better	All	IG1	p17 (12)	801	702	NR	NR	FU=50.5 (40.9)	FU=47.5 (17.6)	3 (1.2 to 4.8)	0.002	No
Morrell, 2009[35] (PP)	SF-12 PCS	Better	All	IG1	p26 (20)	1694	885	51.4 (8)	50.5 (8.7)	3.3 (7.2)	4 (7.9)	0.2 (-0.3 to 0.7)	0.469	Yes
	SF-12 MCS	Better	All	IG1	p26 (20)	1694	885	42.9 (9.3)	42.7 (9.5)	6 (9.4)	4.9 (10)	1.5 (0.3 to 2.6)	0.010	Yes
	QALYs gained		All	IG1	p26 (20)	1712	903	NR	NR	FU=0 (NR)	FU=0 (NR)	0 (0 to 0)	NR	NA
	SF-12	Better	EPDS	IG1	p26	263	142	29.1	29.4	13.2	8.4	4.7	0.001	Yes

Appendix E Table 8. Quality of Life and Functioning Outcomes for Studies of Depression Screening (KQ1)

Author, Year (Pop)	Measure	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
	MCS		≥12 at p06		(20)			(8)	(9.2)	(9.7)	(10.7)	(1.8 to 7.6)		
	QALYs gained		EPDS ≥12 at p06	IG1	p26 (20)	266	144	NR	NR	FU=0 (NR)	FU=0 (NR)	0 (0 to 0)	NR	NA
	SF-12 PCS	Better	EPDS ≥12 at p06	IG1	p26 (20)	263	142	50.1 (9.4)	48.5 (10.9)	2.9 (8.6)	5.8 (10.1)	-1.4 (-3.5 to 0.7)	0.204	Yes
van der Zee, 2017[38] (PP)	SF-12 PCS	Better	All	IG1	p52	1843	1246	NR	NR	FU=52.4 (NR)	FU=52.8 (NR)	-0.5 (-1.3 to 0.2)	0.07	Yes
	SF-12 MCS	Better	All	IG1	p52	1843	1246	NR	NR	FU=51.7 (NR)	FU=49.2 (NR)	2.2 (1.3 to 3)	<0.001	Yes

Abbreviations: Adj = adjusted; BL = baseline; CG = control group; CI = confidence interval; Diff = difference; dx = diagnosis; FUP = followup; g = weeks' gestation; G = general adults; IG = intervention group; NR = not reported; O = older adults; p = weeks postpartum; Pop = population; PP = postpartum population; Pr = pregnant population; QALY = quality-adjusted life year; SD = standard deviation; SF MCS = Short Form Mental Component Score; SF PCS = Short Form Physical Component Score; wks = weeks.

Appendix E Table 9. Functioning Outcomes Results for Studies of Depression Screening (KQ1)

Author, Year (Pop)	Outcome	Measure	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Leung, 2011[33] (PP)	Family functioning	PSI-PD	Better	All	IG1	p26 (18)	231	231	NR	NR	FU=29.9 (2.3)	FU=31.1 (6.9)	NR	0.063	No
	Family functioning	PSI-PCD	Better	All	IG1	p26 (18)	231	231	NR	NR	FU=24.8 (1.8)	FU=25.9 (6.2)	NR	0.050	No
	Family functioning	Chinese Kansas marital satisfaction score	Better	All	IG1	p26 (18)	231	231	17.4 (2.8)	17.3 (2.7)	-0.4 (4.3)	-0.9 (3.1)	0.4 (-0.3 to 1.1)	0.093	No
	Family functioning	PSI	Better	All	IG1	p26 (18)	231	231	NR	NR	FU=80.9 (5.5)	FU=83.7 (16.3)	NR	0.065	No
	Family functioning	PSI-DC	Better	All	IG1	p26 (18)	231	231	NR	NR	FU=26.2 (4.4)	FU=26.7 (6.2)	NR	0.397	No
	Family functioning	PSI	Better	All	IG1	p78	231	231	NR	NR	FU=87.1 (9.5)	FU=89.3 (17.4)	NR	0.187	No
	Family functioning	PSI-PCD	Better	All	IG1	p78	231	231	NR	NR	FU=26.6 (3.1)	FU=27.6 (6.9)	NR	0.112	No
	Family functioning	PSI-PD	Better	All	IG1	p78	231	231	NR	NR	FU=31.6 (5.1)	FU=32.1 (6.9)	NR	0.426	No
	Family functioning	Chinese Kansas marital satisfaction score	Better	All	IG1	p78	231	231	17.4 (2.8)	17.3 (2.7)	-1 (3.2)	-1.1 (2.9)	0.1 (-0.5 to 0.6)	0.636	No
	Family functioning	PSI-DC	Better	All	IG1	p78	231	231	NR	NR	FU=29.5 (5.9)	FU=29.7 (7)	NR	0.654	No
Morrell, 2009[35] (PP)	Family functioning	PSI-DC	Better	All	IG1	p26 (20)	1365	740	NR	NR	FU=53.3 (5.6)	FU=52.8 (6)	0.5 (0 to 1.1)	0.054	Yes
	Family functioning	PSI-PCD	Better	All	IG1	p26 (20)	1435	776	NR	NR	FU=57.1 (4.5)	FU=56.9 (4.8)	0.3 (-0.1 to 0.6)	0.178	Yes
	Family functioning	PSI-PD	Worse	All	IG1	p26 (20)	1422	766	NR	NR	FU=47.4 (8.6)	FU=46.3 (9)	1.2 (0.4 to 2)	0.003	Yes

Appendix E Table 9. Functioning Outcomes Results for Studies of Depression Screening (KQ1)

Author, Year (Pop)	Outcome	Measure	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
	Family functioning	PSI	Better	All	IG1	p26 (20)	1310	698	NR	NR	FU=157.9 (15.3)	FU=155.9 (16.9)	2.1 (0.3 to 3.9)	0.021	Yes
	Family functioning	PSI	Better	EPDS ≥12 at p06	IG1	p26 (20)	211	106	NR	NR	FU=148.9 (17)	FU=139.6 (50.4)	9.2 (4.8 to 13.7)	0.001	Yes
	Family functioning	PSI-DC	Better	EPDS ≥12 at p06	IG1	p26 (20)	217	113	NR	NR	FU=51.5 (6.9)	FU=48.1 (7.7)	2.9 (1.7 to 4.2)	0.001	Yes
	Family functioning	PSI-PD	Worse	EPDS ≥12 at p06	IG1	p26 (20)	229	114	NR	NR	FU=41.3 (8.8)	FU=38.1 (9.5)	3.5 (1.3 to 5.8)	0.002	Yes
	Family functioning	PSI-PCD	Better	EPDS ≥12 at p06	IG1	p26 (20)	231	118	NR	NR	FU=55.7 (5.8)	FU=53.6 (6.9)	2.1 (0.7 to 3.5)	0.003	Yes
Bijl, 2003[28] (O)	Functioning	ADL	Better	All	IG1	8	70	75	9.5 (NR)	9.6 (NR)	1.7 (NR)	1.9 (NR)	NR	NR, NSD	Yes
	Functioning	ADL	Better	All	IG1	26	70	75	9.5 ()	9.6 (NR)	-0.3 (NR)	0 (NR)	NR	NR, NSD	Yes
	Functioning	ADL	Better	All	IG1	52	70	75	9.5 (NR)	9.6 (NR)	-0.1 (NR)	0 (NR)	NR	NR, NSD	Yes
Callahan, 1994[29] (O)	Functioning	SIP	Worse	All	IG1	26	76	60	33 (NR)	29.9 (NR)	-3.7 (NR)	-5 (NR)	NR	NR, NSD	No
	Functioning	SIP	Worse	All	IG1	39	NR	NR	33 (NR)	29.9 (NR)	-5.6 (NR)	-6.1 (NR)	NR	NR, NSD	No
Morrell, 2009[35] (PP)	Functioning	CORE-OM functioning	Worse	All	IG1	p26 (20)	1735	905	(NR)	(NR)	FU=0.5 (0.6)	FU=0.6 (0.7)	-0.1 (-0.1 to 0)	0.001	Yes
	Functioning	CORE-OM functioning	Worse	EPDS ≥12 at p06	IG1	p26 (20)	269	146	NR	NR	FU=1 (0.8)	FU=1.2 (0.8)	0 (-0.4 to	0.001	Yes

Appendix E Table 9. Functioning Outcomes Results for Studies of Depression Screening (KQ1)

Author, Year (Pop)	Outcome	Measure	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
													-0.1)		

Abbreviations: ADL = activities of daily living; Adj = adjusted; BL = baseline; CG = control group; CI = confidence interval; CORE-OM = Clinical Outcomes Routine Evaluation – Outcome Measure; DAS = Disability Assessment Score; DC = difficult child; Diff = difference; dx = diagnosis; EPDS = Edinburgh Postnatal Depression Scale; FUP = followup; g = weeks' gestation; G = general adults; IG = intervention group; NR = not reported; O = older adults; p = weeks postpartum; PP = postpartum population; Pr = pregnant population; PD = parental distress; PCDI = parent–child dysfunctional interaction; PSI = Parenting Stress Index; SD = standard deviation; wks = weeks.

Appendix E Table 10. Other Health Outcomes for Studies of Depression Screening (KQ1), Dichotomous Measures

Author, Year (Pop)	Outcome	Measure	IG	Analyzed	FUP, wks	OR (95% CI)	IG n/N (%)	CG n/N (%)	p-value	Adj
van der Weele, 2012[37] (O)	All-cause mortality	All-cause mortality	IG1	All	52	0.36 (0.15 to 0.92)	7/121 (5.8)	17/118 (14.4)	NR	Yes
	Suicide deaths	Suicide death	IG1	All	52	0.32 (0.01 to 7.99)	0/121 (0.0)	1/118 (0.8)	NR	NR
Yawn, 2012[43] (PP)	Suicide deaths	Suicide death	IG1	All	p52 (44)	0.73 (0.01 to 36.91)	0/1353 (0.0)	0/990 (0.0)	NR	NR
	Family functioning	DAS-6 in bottom 10%	IG1	EPDS ≥10 at BL	p52 (44)	0.24 (0.05 to 1.18)	2/322 (2.0)	6/233 (5.0)	0.30	NR
	Family functioning	PSI >74	IG1	EPDS ≥10 at BL	p52 (44)	0.65 (0.47 to 0.92)	128/322 (72.0)	117/233 (74.0)	0.82	NR

Abbreviations: Adj = adjusted; BL = baseline; CG = control group; CI = confidence interval; DAS = disability assessment score; Diff = difference; dx = diagnosis; EPDS = Edinburgh Postnatal Depression Scale; FUP = followup; g = weeks' gestation; IG = intervention group; NR = not reported; O = older adults; p = weeks postpartum; PP = postpartum population; PSI = Parenting Stress Index; SD = standard deviation; wks = weeks.

Appendix E Table 11. Other Health Outcomes for Studies of Depression Screening (KQ1), Continuous Measures

Author, Year (Pop)	Outcome	Measure	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Leung, 2011[33] (PP)	Child/Infant Outcomes	Body weight (kg)	Worse	All	IG1	p26 (18)	231	231	NR	NR	FU=7.7 (1)	FU=7.7 (0.8)	NR	0.504	No
	Child/Infant Outcomes	Hospitalizations	Worse	All	IG1	p26 (18)	231	231	NR	NR	FU=0.4 (0.9)	FU=0.3 (0.7)	NR	0.518	No
	Child/Infant Outcomes	Hospitalizations	Worse	All	IG1	p78	231	231	NR	NR	FU=0.4 (0.7)	FU=0.4 (0.7)	NR	0.772	No
	Child/Infant Outcomes	Body weight (kg)	Worse	All	IG1	p78	231	231	NR	NR	FU=10.8 (1.2)	FU=10.7 (1)	NR	0.563	No
van der Zee, 2017[38] (PP)	Child/Infant Outcomes	ASQ-SE	Worse	All	IG1	p52	1843	1246	NR	NR	FU=13 (NR)	FU=14.4 (NR)	-1.1 (-2.1 to 0)	0.02	Yes
Morrell, 2009[35] (PP)	ED or inpt utilization	A and E attendances	Worse	All	IG1	p26 (20)	1237	495	NR	NR	FU=0 (NR)	FU=0 (NR)	0 (NR)	NR	NA
	ED or inpt utilization	A and E attendances	Worse	EPDS ≥12 at p06	IG1	p26 (20)	195	78	NR	NR	FU=0 (NR)	FU=0 (NR)	0 (NR)	NR	NA

Abbreviations: Adj = adjusted; ASQ-SE = Ages and Stages Questionnaire- Social Emotional; BL = baseline; CG = control group; CI = confidence interval; Diff = difference; dx = diagnosis; ED = emergency department; FUP = followup; g = weeks' gestation; IG = intervention group; kg = kilograms; NR = not reported; p = weeks postpartum; PP = postpartum; SD = standard deviation; wks = weeks.

Appendix E Table 12. Test Accuracy of the Geriatric Depression Scale to Detect MDD or Depression (KQ2)

Screening test	Author, year	Condition	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
GDS-1	van Marwijk, 1995[44]	MDD	NA	0.18 (0.09, 0.34*)	0.92 (0.90, 0.94*)	0.13 (0.06, 0.25*)	0.95 (0.93, 0.97*)	NR
GDS-4	van Marwijk, 1995[44]	MDD	≥1	0.61 (0.44, 0.75*)	0.72 (0.68, 0.76*)	0.11 (0.08, 0.17*)	0.97 (0.95, 0.98*)	NR
	van Marwijk, 1995[44]	MDD	≥2	0.67 (0.50, 0.80*)	0.66 (0.62, 0.70*)	0.10 (0.07, 0.15*)	0.97 (0.95, 0.98*)	NR
GDS-5	Eriksen, 2019[45]	Any symptom of depression	≥2	0.73 (0.60, 0.83*)	0.73 (0.65, 0.80*)	0.53 (0.42, 0.63*)	0.87 (0.80, 0.92*)	0.81 (0.75, 0.87)
	Izal, 2010[46]	MDD	≥2	0.67 (0.30, 0.92)	0.78 (0.68, 0.86)	0.22 (0.09, 0.42)	0.96 (0.89, 0.99)	0.82 (0.68, 0.95)
GDS-7	Broekman, 2011[47]	MDD	≥2	0.93 (0.88, 0.97)	0.91 (0.90, 0.92)	0.27 (0.23, 0.31)	1.0 (0.99, 1.0)	0.99 (0.98, 1.0)
GDS-R	Izal, 2010[46]	MDD	≥5	1.0 (0.662, 1.0)	0.98 (0.93, 1.0)	0.82 (0.48, 0.97)	1.0 (0.96, 1.0)	0.99 (0.95, 1.0)
GDS-10	van Marwijk, 1995[44]	MDD	≥2	0.67 (0.50, 0.80*)	0.66 (0.62, 0.70*)	0.10 (0.07, 0.15*)	0.97 (0.95, 0.98*)	NR
	Izal, 2010[46]	MDD	≥3	1.0 (0.66, 1.0)	0.81 (0.72, 0.88)	0.33 (0.17, 0.54)	1.0 (0.95, 1.0)	0.95 (0.89, 0.98)
	van Marwijk, 1995[44]	MDD	≥3	0.52 (0.35, 0.67*)	0.83 (0.80, 0.86*)	0.15 (0.10, 0.23*)	0.97 (0.95, 0.98*)	NR
GDS-15	Marc, 2008[48]	MDD	≥0	1.0 (0.95, 1.0*)	0.0 (0, 0.01*)	0.14 (0.12, 0.18*)	NA	0.793 (0.733, 0.854)
	Alves Apostolo, 2018[49]	MDD	≥0.5	1.0 (0.86, 1.0*)	0.17 (0.11, 0.25*)	0.19 (0.13, 0.27)*	1.0 (0.84, 1.0)*	NR
	Marc, 2008[48]	MDD	≥1	0.97 (0.90, 0.99*)	0.15 (0.12, 0.18*)	0.16 (0.13, 0.20)*	0.97 (0.89, 0.99)*	0.793 (0.733, 0.854)
	Alves Apostolo, 2018[49]	MDD	≥1.5	1.0 (0.86, 1.00)*	0.32 (0.24, 0.41)*	0.23 (0.16, 0.32)*	1.0 (0.91, 1.0)*	NR
	Marc, 2008[48]	MDD	≥2	0.93 (0.85, 0.97*)	0.34 (0.30, 0.39*)	0.19 (0.15, 0.24)*	0.97 (0.92, 0.99)*	0.793 (0.733, 0.854)
	van Marwijk, 1995[44]	MDD	≥2	0.76 (0.59, 0.87*)	0.53 (0.49, 0.57*)	0.09 (0.06, 0.13*)	0.97 (0.95, 0.99*)	NR
	Alves Apostolo, 2018[49]	MDD	≥2.5	1.0 (0.86, 1.0*)	0.38 (0.30, 0.47*)	0.24 (0.17, 0.34)*	1.0 (0.92, 1.0)*	NR
	Jung, 2019[50]	Any depressive disorder	≥3	0.94 (0.90, 0.97*)	0.64 (0.58, 0.71*)	0.69 (0.62, 0.74*)	0.93 (0.88, 0.96*)	0.896 (0.015)
	Marc, 2008[48]	MDD	≥3	0.83	0.51	0.22	0.95	0.793

Appendix E Table 12. Test Accuracy of the Geriatric Depression Scale to Detect MDD or Depression (KQ2)

Screening test	Author, year	Condition	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
				(0.73, 0.90*)	(0.47, 0.56*)	(0.18, 0.28)*	(0.91, 0.97)*	(0.733, 0.854)
	van Marwijk, 1995[44]	MDD	≥3	0.67 (0.50, 0.80*)	0.73 (0.69, 0.76*)	0.13 (0.08, 0.18*)	0.97 (0.95, 0.99)*	NR
	Alves Apostolo, 2018[49]	MDD	≥3.5	0.96 (0.79, 0.99*)	0.46 (0.37, 0.55*)	0.26 (0.18, 0.36)*	0.98 (0.90, 1.0)*	NR
	Jung, 2019[50]	MDD	≥4	1.0 (0.92, 1.0*)	0.60 (0.54, 0.65*)	0.25 (0.19, 0.31*)	1.00 (0.98, 1.00)*	0.923 (0.016)
	Jung, 2019[50]	Any depressive disorder	≥4	0.80 (0.74, 0.86*)	0.80 (0.74, 0.85*)	0.77 (0.70, 0.82*)	0.83 (0.78, 0.88)*	0.896 (0.015)
	Marc, 2008[48]	MDD	≥4	0.76 (0.65, 0.84*)	0.65 (0.60, 0.69*)	0.27 (0.21, 0.33*)	0.94 (0.91, 0.96)*	0.793 (0.733, 0.854)
	Pellas, 2021[51]	MDE	≥4	1.0 (0.80, 1.0)	0.76 (0.66, 0.84)	0.42 (0.28, 0.58)*	1.0 (0.95,1.0)*	0.97 (NR)
	Rait, 1999[52]	GMS depression score ≥3	≥4	0.92 (0.64, 1.0)	0.71 (0.63, 0.79)	0.26 (0.16, 0.40)*	0.99 (0.94, 1.0)*	NR
	Alves Apostolo, 2018[49]	MDD	≥4.5	0.96 (0.79, 0.99*)	0.53 (0.44, 0.61*)	0.29 (0.20, 0.39)*	0.98 (0.91, 1.0)*	NR
	Broekman, 2011[47]	MDD	≥5	0.97 (0.94, 1.0)	0.95 (0.95, 0.96)	0.42 (0.37, 0.47)	1.0 (1.0, 1.0)	0.98 (0.97, 0.99)
	Davison, 2009[53]	MDD	≥5	0.93 (0.76, 0.99)	0.77 (0.69, 0.84)	0.44 (0.32, 0.57)*	0.98 (0.94,1.0)*	NR
	Izal, 2010[46]	MDD	≥5	1.0 (0.66, 1.0)	0.88 (0.79, 0.93)	0.43 (0.22, 0.66)	1.0 (0.96, 1.0)	0.97 (0.91, 0.99)
	Jung, 2019[50]	Any depressive disorder	≥5	0.62 (0.54, 0.68*)	0.91 (0.86, 0.94*)	0.85 (0.78, 0.90)*	0.74 (0.68, 0.79)*	0.896 (0.015)
	Jung, 2019[50]	MDD	≥5	0.91 (0.79, 0.96*)	0.75 (0.70, 0.79*)	0.32 (0.25, 0.41)*	0.98 (0.96, 0.99)*	0.92 (0.016)
	Licht-Strunk, 2005[54]	MDD†	≥5	0.58 (0.54, 0.62)*	0.91 (0.90, 0.91)*	0.47 (0.43, 0.50)*	0.94 (0.93, 0.94)*	NR
	Marc, 2008[48]	MDD	≥5	0.72 (0.60, 0.81*)	0.78 (0.74, 0.82*)	0.36 (0.28, 0.44)*	0.94 (0.91, 0.96)*	0.793 (0.733, 0.854)
	Pellas, 2021[51]	MDE	≥5	1.0 (0.80, 1.0)	0.81 (0.72, 0.88)	0.49 (0.33, 0.64)*	1.0 (0.95, 1.0)*	0.97 (NR)
	Alves Apostolo, 2018[49]	MDD	≥5.5	0.78 (0.58, 0.90*)	0.58 (0.49, 0.66*)	0.27 (0.18, 0.39)*	0.93 (0.85, 0.97)*	NR
	Blank, 2004[55]	MDD	≥6	0.79 (0.51, 0.94)	0.75 (0.71, 0.77)	0.28 (0.17, 0.44)*	0.97 (0.90, 0.99)*	0.81 (0.76, 0.96)

Appendix E Table 12. Test Accuracy of the Geriatric Depression Scale to Detect MDD or Depression (KQ2)

Screening test	Author, year	Condition	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
	Davison, 2009[53]	MDD	≥6	0.85 (0.66, 0.96)	0.84 (0.76, 0.89)	0.50 (0.36, 0.64)*	0.97 (0.92, 0.99)*	NR
	Jung, 2019[50]	MDD	≥6	0.89 (0.77, 0.95*)	0.82 (0.78, 0.86*)	0.40 (0.31, 0.50*)	0.98 (0.96, 0.99*)	0.923 (0.016)
	Jung, 2019[50]	Any depressive disorder	≥6	0.50 (0.43, 0.57*)	0.94 (0.90, 0.96*)	0.87 (0.79, 0.92*)	0.70 (0.64, 0.75*)	0.896 (0.015)
	Marc, 2008[48]	MDD	≥6	0.61 (0.49, 0.71*)	0.86 (0.83, 0.89*)	0.43 (0.33, 0.52)*	0.93 (0.90, 0.95)*	0.793 (0.733, 0.854)
	Pellas, 2021[51]	MDE	≥6	0.94 (0.71, 1.0)	0.88 (0.79, 0.93)	0.57 (0.39, 0.73)*	0.99 (0.94, 1.0)*	0.97 (NR)
	Alves Apostolo, 2018[49]	MDD	≥6.5	0.74 (0.54, 0.87*)	0.64 (0.55, 0.72*)	0.29 (0.19, 0.41)*	0.93 (0.85, 0.97)*	NR
	Jung, 2019[50]	MDD	≥7	0.80 (0.66, 0.89*)	0.91 (0.88, 0.94*)	0.54 (0.43, 0.66*)	0.97 (0.95, 0.99*)	0.923 (0.016)
	Marc, 2008[48]	MDD	≥7	0.55 (0.43, 0.66*)	0.91 (0.88, 0.94*)	0.51 (0.40, 0.62)*	0.92 (0.89, 0.94*)	0.793 (0.733, 0.854)
	Pellas, 2021[51]	MDE	≥7	0.88 (0.64, 0.99)	0.91 (0.83, 0.96)	0.62 (0.43, 0.79)*	0.98 (0.92, 0.99)*	0.97 (NR)
	Alves Apostolo, 2018[49]	MDD	≥7.5	0.57 (0.37, 0.74*)	0.70 (0.61, 0.77*)	0.27 (0.17, 0.41)*	0.89 (0.81, 0.94)*	NR
	Marc, 2008[48]	MDD	≥8	0.38 (0.28, 0.50*)	0.93 (0.90, 0.95*)	0.48 (0.36, 0.61)*	0.90 (0.87, 0.92)*	0.793 (0.733, 0.854)
	Pellas, 2021[51]	MDE	≥8	0.82 (0.57, 96)	0.93 (0.86, 0.97)	0.67 (0.45,0.83)*	0.97 (0.91, 0.99)*	0.97 (NR)
	Shin, 2019[56]	MDD	≥8	0.90 (0.74, 0.97*)	0.88 (0.86, 0.90*)	0.23 (0.17, 0.32*)	0.99 (0.99, 1.0*)	0.93 (NR)
	Alves Apostolo, 2018[49]	MDD	≥8.5	0.52 (0.33, 0.71*)	0.72 (0.64, 0.80*)	0.27 (0.16, 0.42)*	0.88 (0.80, 0.93)*	NR
	Blank, 2004[55]	MDD	≥9	0.71 (0.45, 0.90)	0.91 (0.88, 0.93)	0.08 (0.05, 0.15)*	0.96 (0.91, 0.99)*	NR
	Marc, 2008[48]	MDD	≥9	0.25 (0.17, 0.37*)	0.95 (0.93, 0.97*)	0.49 (0.33, 0.64)*	0.88 (0.85, 0.91)*	0.793 (0.733, 0.854)
	Pellas, 2021[51]	MDE	≥9	0.71 (0.44, 90)	0.97 (0.91, 0.99)	0.80 (0.55, 0.93)*	0.95 (0.89, 0.98)*	0.97 (NR)
	Stefan, 2017[57]	MDD	≥9	0.96 (0.80, 0.99*)	0.89 (0.82, 0.93*)	0.58 (0.42, 0.71*)	0.99 (0.96, 1.0*)	NR
	Alves Apostolo,	MDD	≥9.5	0.44	0.86	0.38	0.88	NR

Appendix E Table 12. Test Accuracy of the Geriatric Depression Scale to Detect MDD or Depression (KQ2)

Screening test	Author, year	Condition	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
	2018[49]			(0.26, 0.63*)	(0.79, 0.91*)	(0.22, 0.57)*	(0.81, 0.93)*	
	Marc, 2008[48]	MDD	≥10	0.21 (0.13, 0.32*)	0.97 (0.95, 0.98*)	0.56 (0.37, 0.72)*	0.88 (0.85, 0.91)*	0.793 (0.733, 0.854)
	Stefan, 2017[57]	MDD	≥10	0.79 (0.60, 0.91*)	0.92 (0.87, 0.96*)	0.63 (0.46, 0.78*)	0.96 (0.92, 0.98*)	NR
	Alves Apostolo, 2018[49]	MDD	≥10.5	0.44 (0.26, 0.63*)	0.97 (0.91, 0.99*)	0.71 (0.45, 0.88)*	0.90 (0.83, 0.94)*	NR
	Marc, 2008[48]	MDD	≥11	0.17 (0.10, 0.27*)	0.98 (0.96, 0.99*)	0.60 (0.39, 0.78)*	0.88 (0.84, 0.90)*	0.793 (0.733, 0.854)
	Alves Apostolo, 2018[49]	MDD	≥11.5	0.35 (0.19, 0.55*)	0.97 (0.93, 0.99*)	0.73 (0.43, 0.90)*	0.88 (0.82, 0.93)*	NR
	Marc, 2008[48]	MDD	≥12	0.11 (0.06, 0.21)	0.99 (0.97, 0.99)	0.62 (0.36, 0.82)*	0.87 (0.84, 0.90)*	0.793 (0.733, 0.854)
	Alves Apostolo, 2018[49]	MDD	≥12.5	0.09 (0.02, 0.27*)	0.98 (0.94, 1.0*)	0.50 (0.15, 0.85)*	0.84 (0.77, 0.90)*	NR
	Marc, 2008[48]	MDD	≥13	0.07 (0.02, 0.13*)	0.99 (0.99, 1.0*)	0.71 (0.36, 0.92)*	0.86 (0.83, 0.89)*	0.793 (0.733, 0.854)
	Alves Apostolo, 2018[49]	MDD	≥14	0.04 (0.01, 0.21*)	1.0 (0.97, 1.0*)	1.0 (0.21, 1.0)*	0.84 (0.77, 0.89)*	NR
	Marc, 2008[48]	MDD	≥14	0 (0, 0.05*)	1.0 (0.99, 1.0*)	NA	0.86 (0.82, 0.88)*	0.793 (0.733, 0.854)
GDS-30	van Marwijk, 1995[44]	MDD	≥7	0.79 (0.62, 0.89*)	0.67 (0.62, 0.70*)	0.12 (0.09, 0.17*)	0.98 (0.96, 0.99*)	NR
	Blank, 2004[55]	MDD	≥10	0.79 (0.50, 0.94)	0.67 (0.63, 0.69)	0.23 (0.13, 0.37)*	0.96 (0.89, 0.99)*	0.87 (0.77, 0.97)
	van Marwijk, 1995[44]	MDD	≥11	0.55 (0.38, 0.70*)	0.86 (0.83, 0.89*)	0.19 (0.12, 0.28*)	0.97 (0.95, 0.98*)	NR
	Izal, 2010[46]	MDD	≥15	1.0 (0.66, 1.0)	0.96 (0.90, 0.99)	0.69 (0.39, 0.91)	1.0 (0.96, 1.0)	0.98 (0.93, 1.0)
	Blank, 2004[55]	MDD	≥17	0.79 (0.51, 0.94)	0.87 (0.84, 0.89)	0.44 (0.27, 0.63)*	0.97 (0.92, 0.99)*	0.87 (0.77, 0.97)
	Stefan, 2017[57]	MDD	≥17	1.0 (0.86, 1.0*)	0.89 (0.83, 0.93*)	0.60 (0.45, 0.74*)	1.0 (0.97, 1.0*)	NR
	Stefan, 2017[57]	MDD	≥18	0.88 (0.69, 0.96*)	0.91 (0.85, 0.94*)	0.60 (0.44, 0.74*)	0.98 (0.94, 0.99*)	NR
	Stefan, 2017[57]	MDD	≥19	0.83 (0.64, 0.93*)	0.92 (0.86, 0.95*)	0.63 (0.45, 0.77*)	0.97 (0.93, 0.99*)	NR

Appendix E Table 12. Test Accuracy of the Geriatric Depression Scale to Detect MDD or Depression (KQ2)

* Calculated sensitivity, specificity, PPV, NPV, or confidence interval.
† Adjusted for partial verification.

Abbreviations: AUC = area under curve; CI = confidence interval; GDS = Geriatric Depression Scale; MDD = major depressive disorder; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; SE = standard error.

Appendix E Table 13. Test Accuracy of Screening Tests for Major Depression Reported in ESRs (KQ2)

Screening test	Author, year	Reference standard	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
PHQ-9 Linear	Negeri, 2021[58]	Fully structured diagnostic interview	≥5	0.91 (0.85, 0.95)	0.61 (0.51, 0.69)	0.84
			≥6	0.88 (0.80, 0.93)	0.69 (0.60, 0.76)	
			≥7	0.82 (0.73, 0.89)	0.75 (0.67, 0.82)	
			≥8	0.77 (0.66, 0.86)	0.81 (0.74, 0.86)	
			≥9	0.69 (0.59, 0.78)	0.85 (0.79, 0.90)	
			≥10	0.57 (0.46, 0.67)	0.91 (0.87, 0.94)	
			≥11	0.52 (0.41, 0.63)	0.93 (0.89, 0.95)	
			≥12	0.45 (0.35, 0.56)	0.95 (0.92, 0.97)	
			≥13	0.39 (0.30, 0.50)	0.96 (0.94, 0.97)	
			≥14	0.32 (0.24, 0.41)	0.97 (0.95, 0.98)	
			≥15	0.91 (0.85, 0.95)	0.61 (0.51, 0.69)	
		MINI	≥5	0.96 (0.93, 0.97)	0.60 (0.55, 0.64)	0.88
			≥6	0.92 (0.89, 0.95)	0.68 (0.63, 0.72)	
			≥7	0.88 (0.83, 0.92)	0.74 (0.70, 0.78)	
			≥8	0.85 (0.79, 0.89)	0.80 (0.76, 0.83)	
			≥9	0.80 (0.73, 0.85)	0.85 (0.82, 0.88)	
			≥10	0.67 (0.60, 0.73)	0.91 (0.89, 0.93)	
			≥11	0.61 (0.54, 0.68)	0.93 (0.91, 0.95)	
			≥12	0.55 (0.47, 0.62)	0.95 (0.93, 0.96)	
			≥13	0.47 (0.41, 0.54)	0.96 (0.95, 0.97)	
			≥14	0.40 (0.35, 0.46)	0.97 (0.96, 0.98)	
			≥15	0.96 (0.93, 0.97)	0.60 (0.55, 0.64)	
		Semi-structured diagnostic interview	≥5	0.98 (0.95, 0.99)	0.53 (0.49, 0.58)	0.90
			≥6	0.97 (0.94, 0.98)	0.61 (0.57, 0.65)	
			≥7	0.95 (0.92, 0.98)	0.68 (0.64, 0.72)	
			≥8	0.92 (0.88, 0.95)	0.74 (0.70, 0.77)	
			≥9	0.89 (0.84, 0.92)	0.80 (0.76, 0.82)	
			≥10	0.81 (0.75, 0.86)	0.88 (0.85, 0.90)	
			≥11	0.75 (0.69, 0.80)	0.90 (0.88, 0.92)	
			≥13	0.67 (0.61, 0.72)	0.93 (0.91, 0.94)	
			≥12	0.61 (0.55, 0.67)	0.94 (0.93, 0.96)	
			≥14	0.52 (0.46, 0.58)	0.96 (0.94, 0.97)	
			≥15	0.98 (0.95, 0.99)	0.53 (0.49, 0.58)	
	Wang, 2021[59]	Fully or semi-	≥7	0.82 (0.74, 0.91)	0.77 (0.68, 0.87)	NR

Appendix E Table 13. Test Accuracy of Screening Tests for Major Depression Reported in ESRs (KQ2)

Screening test	Author, year	Reference standard	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
		structured diagnostic interview	≥10	0.81 (NR)	0.79 (NR)	NR
PHQ-9 Algorithm	He, 2020[60]	Fully structured diagnostic interview	Original	0.35 (0.26, 0.46)	0.95 (0.93, 0.97)	NR
			Modified	0.37 (0.27, 0.48)	0.95 (0.92, 0.97)	NR
		MINI	Original	0.51 (0.49, 0.53)	0.97 (0.96, 0.98)	NR
			Modified	0.54 (0.45, 0.64)	0.96 (0.94, 0.97)	NR
		Semi-structured diagnostic interview	Original	0.57 (0.49, 0.64)	0.95 (0.94, 0.97)	NR
			Modified	0.61 (0.54, 0.68)	0.95 (0.93, 0.96)	NR
PHQ-8	Wu, 2020[61]	Fully structured diagnostic interview	≥5	0.92 (0.85, 0.96)	0.57 (0.49, 0.66)	0.852
			≥6	0.88 (0.79, 0.93)	0.65 (0.57, 0.73)	
			≥7	0.83 (0.73, 0.90)	0.72 (0.64, 0.79)	
			≥8	0.77 (0.66, 0.85)	0.78 (0.71, 0.84)	
			≥9	0.69 (0.59, 0.77)	0.83 (0.76, 0.87)	
			≥10	0.63 (0.52, 0.72)	0.86 (0.81, 0.90)	
			≥11	0.57 (0.45, 0.67)	0.89 (0.85, 0.93)	
			≥12	0.51 (0.38, 0.64)	0.92 (0.88, 0.94)	
			≥13	0.43 (0.32, 0.55)	0.94 (0.91, 0.96)	
			≥14	0.36 (0.26, 0.47)	0.95 (0.93, 0.97)	
			≥15	0.30 (0.22, 0.39)	0.96 (0.95, 0.98)	
		MINI	≥5	0.96 (0.93, 0.98)	0.58 (0.50, 0.65)	0.894
			≥6	0.92 (0.85, 0.96)	0.67 (0.59, 0.74)	
			≥7	0.89 (0.81, 0.94)	0.73 (0.67, 0.79)	
			≥8	0.83 (0.75, 0.89)	0.80 (0.75, 0.84)	
			≥9	0.78 (0.69, 0.85)	0.85 (0.81, 0.89)	
			≥10	0.72 (0.63, 0.79)	0.88 (0.84, 0.91)	
			≥11	0.65 (0.57, 0.73)	0.91 (0.88, 0.94)	
			≥12	0.59 (0.51, 0.66)	0.93 (0.91, 0.95)	
			≥13	0.53 (0.44, 0.62)	0.95 (0.93, 0.97)	
			≥14	0.43 (0.35, 0.51)	0.97 (0.95, 0.98)	
			≥15	0.37 (0.29, 0.45)	0.98 (0.96, 0.99)	
		Semi-structured	≥5	0.98 (0.95, 0.99)	0.55 (0.50, 0.60)	0.930

Appendix E Table 13. Test Accuracy of Screening Tests for Major Depression Reported in ESRs (KQ2)

Screening test	Author, year	Reference standard	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
		diagnostic interview	≥6	0.98 (0.95, 0.99)	0.63 (0.58, 0.68)	
			≥7	0.97 (0.93, 0.99)	0.70 (0.66, 0.74)	
			≥8	0.94 (0.89, 0.96)	0.76 (0.72, 0.79)	
			≥9	0.89 (0.84, 0.92)	0.81 (0.78, 0.84)	
			≥10	0.86 (0.80, 0.90)	0.86 (0.83, 0.89)	
			≥11	0.81 (0.75, 0.87)	0.90 (0.87, 0.92)	
			≥12	0.74 (0.68, 0.79)	0.92 (0.89, 0.93)	
			≥13	0.67 (0.60, 0.73)	0.94 (0.92, 0.95)	
			≥14	0.59 (0.53, 0.65)	0.96 (0.94, 0.97)	
			≥15	0.51 (0.44, 0.57)	0.97 (0.95, 0.98)	
PHQ-4	Harel, 2022[62]	Fully structured diagnostic interview	≥1	0.94 (0.88, 0.97)	0.40 (0.30, 0.50)	NR
			≥2	0.88 (0.80, 0.92)	0.60 (0.51, 0.69)	
			≥3	0.78 (0.69, 0.85)	0.74 (0.66, 0.81)	
			≥4	0.68 (0.56, 0.78)	0.85 (0.78, 0.90)	
			≥5	0.54 (0.42, 0.66)	0.91 (0.86, 0.94)	
			≥6	0.41 (0.31, 0.52)	0.95 (0.91, 0.97)	
			≥7	0.30 (0.23, 0.38)	0.97 (0.94, 0.98)	
			≥8	0.22 (0.17, 0.27)	0.98 (0.96, 0.99)	
			≥9	0.15 (0.11, 0.20)	0.99 (0.98, 0.99)	
			≥10	0.07 (0.04, 0.12)	0.99 (0.99, 1.00)	
			≥11	0.04 (0.02, 0.07)	1.00 (0.99, 1.00)	
			≥12	0.03 (0.01, 0.06)	1.00 (1.00, 1.00)	
		MINI	≥1	0.98 (0.96, 0.99)	0.41 (0.36, 0.46)	NR
			≥2	0.95 (0.93, 0.97)	0.59 (0.53, 0.64)	
			≥3	0.89 (0.84, 0.92)	0.72 (0.67, 0.76)	
			≥4	0.80 (0.73, 0.85)	0.83 (0.80, 0.86)	
			≥5	0.67 (0.60, 0.74)	0.90 (0.87, 0.92)	
			≥6	0.54 (0.46, 0.61)	0.94 (0.93, 0.96)	
			≥7	0.41 (0.34, 0.48)	0.97 (0.96, 0.98)	
			≥8	0.30 (0.25, 0.36)	0.99 (0.98, 0.99)	
			≥9	0.21 (0.17, 0.26)	0.99 (0.99, 0.99)	
			≥10	0.12 (0.09, 0.16)	1.00 (0.99, 1.00)	
			≥11	0.08 (0.06, 0.10)	1.00 (1.00, 1.00)	
			≥12	0.04 (0.03, 0.06)	1.00 (1.00, 1.00)	

Appendix E Table 13. Test Accuracy of Screening Tests for Major Depression Reported in ESRs (KQ2)

Screening test	Author, year	Reference standard	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
		Semi-structured diagnostic interview	≥1	1.00 (0.91, 1.00)	0.35 (0.30, 0.40)	NR
			≥2	0.98 (0.95, 1.00)	0.52 (0.46, 0.57)	
			≥3	0.97 (0.92, 0.99)	0.66 (0.61, 0.71)	
			≥4	0.88 (0.81, 0.93)	0.79 (0.74, 0.83)	
			≥5	0.80 (0.73, 0.86)	0.87 (0.84, 0.90)	
			≥6	0.66 (0.58, 0.74)	0.92 (0.89, 0.94)	
			≥7	0.52 (0.43, 0.60)	0.95 (0.93, 0.97)	
			≥8	0.38 (0.30, 0.46)	0.97 (0.96, 0.98)	
			≥9	0.28 (0.22, 0.35)	0.99 (0.98, 0.99)	
			≥10	0.18 (0.13, 0.24)	0.99 (0.99, 1.00)	
			≥11	0.11 (0.08, 0.16)	1.00 (0.99, 1.00)	
			≥12	0.07 (0.05, 0.11)	1.00 (1.00, 1.00)	
PHQ-2	Levis, 2020[63]	Fully structured diagnostic interview	≥1	0.93 (0.88, 0.96)	0.48 (0.38, 0.58)	0.82 (0.81, 0.84)
			≥2	0.82 (0.75, 0.87)	0.71 (0.63, 0.77)	
			≥3	0.53 (0.44, 0.62)	0.89 (0.84, 0.92)	
			≥4	0.36 (0.30, 0.43)	0.94 (0.92, 0.96)	
			≥5	0.21 (0.16, 0.26)	0.98 (0.97, 0.99)	
			≥6	0.13 (0.09, 0.17)	0.99 (0.98, 0.99)	
		MINI	≥1	0.96 (0.94, 0.98)	0.48 (0.43, 0.53)	0.87 (0.85, 0.88)
			≥2	0.89 (0.84, 0.92)	0.68 (0.64, 0.73)	
			≥3	0.69 (0.62, 0.75)	0.87 (0.84, 0.90)	
			≥4	0.50 (0.44, 0.56)	0.94 (0.93, 0.96)	
			≥5	0.30 (0.25, 0.36)	0.98 (0.97, 0.98)	
			≥6	0.18 (0.15, 0.22)	0.99 (0.99, 0.99)	
		Semi-structured diagnostic interview	≥1	0.98 (0.96, 0.99)	0.46 (0.42, 0.51)	0.88 (0.86, 0.89)
			≥2	0.91 (0.88, 0.94)	0.67 (0.64, 0.71)	
			≥3	0.72 (0.67, 0.77)	0.85 (0.83, 0.87)	
			≥4	0.55 (0.50, 0.61)	0.93 (0.91, 0.94)	
			≥5	0.35 (0.31, 0.40)	0.97 (0.96, 0.98)	
			≥6	0.23 (0.19, 0.27)	0.99 (0.98, 0.99)	
PHQ-2 + PHQ-9	Levis, 2020[63]	Semi-structured diagnostic interview	≥2 (PHQ-2), ≥10 (PHQ-9)	0.82 (0.76, 0.86)	0.87 (0.84, 0.89)	NR
			≥3 (PHQ-2), ≥10 (PHQ-9)	0.70 (0.64, 0.75)	0.91 (0.89, 0.93)	NR

Appendix E Table 13. Test Accuracy of Screening Tests for Major Depression Reported in ESRs (KQ2)

Screening test	Author, year	Reference standard	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
Whooley	Bosanquet, 2015[64]	Diagnostic interview	NA	0.95 (0.88, 0.97)	0.65 (0.56, 0.74)	NR
	Smith, 2022[65]	Diagnostic interview	NA	0.95 (0.81, 0.99)	0.60 (0.44, 0.74)	0.87
CES-D	Vilagut, 2016[66]	Standardized diagnostic interview	≥20	0.83 (0.75, 0.89)	0.78 (0.71, 0.83)	0.87
			≥16	0.87 (0.82, 0.91)	0.70 (0.65, 0.75)	
			≥22	0.79 (0.69, 0.85)	0.80 (0.75, 0.85)	
EPDS	Levis, 2020[67]	Fully structured diagnostic interview	≥7	0.95 (0.71, 0.99)	0.57 (0.36, 0.76)	0.924
			≥8	0.95 (0.70, 0.99)	0.62 (0.41, 0.80)	
			≥9	0.95 (0.64, 1.00)	0.71 (0.50, 0.85)	
			≥10	0.93 (0.64, 0.99)	0.78 (0.57, 0.90)	
			≥11	0.90 (0.58, 0.98)	0.83 (0.62, 0.94)	
			≥12	0.81 (0.56, 0.94)	0.86 (0.70, 0.94)	
			≥13	0.79 (0.50, 0.94)	0.90 (0.75, 0.96)	
			≥14	0.77 (0.43, 0.94)	0.93 (0.82, 0.98)	
			≥15	0.66 (0.37, 0.87)	0.95 (0.86, 0.99)	
		MINI	≥7	0.95 (0.89, 0.98)	0.60 (0.52, 0.67)	0.890
			≥8	0.91 (0.85, 0.95)	0.67 (0.60, 0.74)	
			≥9	0.88 (0.80, 0.93)	0.74 (0.66, 0.80)	
			≥10	0.84 (0.74, 0.91)	0.79 (0.73, 0.84)	
			≥11	0.82 (0.71, 0.89)	0.84 (0.79, 0.89)	
			≥12	0.74 (0.60, 0.85)	0.89 (0.83, 0.92)	
			≥13	0.69 (0.54, 0.81)	0.91 (0.87, 0.94)	
			≥14	0.60 (0.45, 0.73)	0.94 (0.91, 0.96)	
			≥15	0.52 (0.39, 0.64)	0.95 (0.92, 0.97)	
		Semi-structured diagnostic interview	≥7	0.95 (0.91, 0.97)	0.65 (0.58, 0.71)	0.915
			≥8	0.92 (0.87, 0.95)	0.72 (0.66, 0.78)	
			≥9	0.89 (0.83, 0.93)	0.78 (0.73, 0.83)	
			≥10	0.85 (0.79, 0.90)	0.84 (0.79, 0.88)	
			≥11	0.81 (0.75, 0.87)	0.88 (0.85, 0.91)	
			≥12	0.75 (0.67, 0.81)	0.92 (0.89, 0.94)	
			≥13	0.66 (0.58, 0.74)	0.95 (0.92, 0.96)	
			≥14	0.58 (0.50, 0.66)	0.96 (0.95, 0.98)	
			≥15	0.51 (0.44, 0.58)	0.97 (0.96, 0.98)	

Appendix E Table 13. Test Accuracy of Screening Tests for Major Depression Reported in ESRs (KQ2)

Abbreviations: AUC = area under the curve; CES-D = Center for Epidemiologic Studies Depression scale; CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale; MINI = Mini International Neuropsychiatric Interview; PHQ = Patient Health Questionnaire.

Appendix E Table 14. Adverse Events for Studies of Depression Screening (KQ3)

Author, Year (Pop)	Measure	IG	Analyzed	FUP, wks	OR (95% CI)	IG n/N (%)	CG n/N (%)	p-value	Adj
Leung, 2011[33] (PP)	Adverse events (any)	IG1	All	p78	1 (0.02 to 50.61)	0/231 (0.0)	0/231 (0.0)	NR	NA

Abbreviations: Adj = adjusted; CG = control group; FUP = followup; IG = intervention group; OR = odds ratio; p = weeks postpartum; PP = perinatal population.

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Aherne, 2017[68]	Studies that included the treatment of moderate depression solely	RCTs and systematic reviews that investigated pharmacotherapy, psychotherapy alone, and pharmacotherapy and psychotherapy combined, with moderate depression alone	NR	NR	NR
Castro, 2020[69]	Adults (age ≥18 years) with major depression using ICD, DSM, or significant (moderate to severe) depressive symptoms established using a validated screening measure	Telephone-administered of any kind of psychotherapy; contact between therapist and patient had to be at least 90% over the telephone and aim of the intervention was to reduce depressive symptomatology	Control condition (e.g., waiting-list control, treatment as usual) or an active treatment (psychological or pharmacological)	Any setting	Included trials that used variety of depression instruments: BDI, PHQ-9, POMs, MADRS, QIDS, CES-D, and SCL-20.
Collado, 2016[70]	Studies must comprise an adult sample (age ≥18 years), include a sample of Latinos exclusively, or conduct analyses to determine whether Latino ethnicity moderated treatment results, or compare outcome differences between Latinos and individuals of other ethnicities, or include ethnicity as a covariate	Study must focus on the evaluation of a depression psychotherapy, focus on depressive symptoms or depression, describe pre- and post-treatment depression outcomes	NR	Studies have been conducted in the US, US territories, or US border with Mexico or Canada	NR

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Cuijpers, 2017[71]	Adults with depression; depression could be established with a diagnostic interview or with a score above a cutoff on a self-report measure.	Randomized trial in which a psychotherapy for adult depression was tested; allowed any treatment format.	Compared with a control group (waiting list, care-as-usual, placebo, other inactive treatment) or another treatment (psychological or pharmacological)	NR	Compiled results for all outcomes they have examined, including depression sx, other mental health, QoL, functioning, suicide-related, maternal.
Cuijpers, 2018a[72]	Depression had to be defined according to a diagnostic interview in which a depressive disorder was established, or as a score above a cutoff on a self-rating depression scale. Studies in adults only.	Psychological treatment of depression	Waiting list, care-as-usual, placebo, or other control. Studies in which psychotherapy was compared with another active treatment (e.g., pharmacotherapy, another psychotherapy) were not included.	NR	We only used those instruments that explicitly measured symptoms of depression, such as the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) or the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960). If more than one depression measure was used, the mean of the effect sizes was calculated, so that each comparison provided only one effect size.
Cuijpers, 2019a[73]	Adults (age >18 years) with a depressive disorder according to a diagnostic interview or an elevated level of depressive symptomatology (as indicated by a score above a cutoff score	All randomized trials in which at least one arm was a psychological treatment for adults	Required a control group (WL, UC, placebo, or similar).	NR	Only included outcome measures that assess depressive symptoms.

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
	on a validated self-report depression scale).				
Cuijpers, 2019b[74]	Adults suffering from depression. A diagnosis of depression could be established with a diagnostic interview or with a score above a cutoff on a self-report measure.	Psychological treatment	Care as usual: (1) CAU in primary care, meaning that patients were recruited from primary care and receiving the usual care given in that context; (2) CAU in specialized mental health care; (3) CAU in perinatal care; (4) CAU in general medical care (in patients with comorbid general medical disorders); and (5) no treatment. In the case of no treatment, we did allow minimal support from the study, like sharing the results of the screening, advise to seek treatment elsewhere, information booklets, or one information session.	Outpatient only	We used all measures examining depressive symptoms, such as the Beck Depression Inventory/BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961); the BDI-II (Beck, Steer, & Brown, 1996); or the Hamilton Rating Scale for Depression/HAMD-17 (Hamilton, 1960). When more than one depression measure was used in a study, we pooled the outcomes within a study.
Cuijpers, 2020[75]	Adults with depression; depression could be established with a diagnostic interview or with a score above a cutoff on a self-report measure.	Randomized trial in which a psychotherapy for adult depression was tested; allowed any treatment format.	Compared with a control group (waiting list, care-as-usual, placebo, other inactive treatment) or another treatment (psychological or pharmacological)	NR	Used all measures examining depressive symptoms (such as the Beck Depression Inventory/BDI; the BDI-II; or the Hamilton Rating Scale for Depression/HAMD-17)

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Driessen, 2015[76]	Adults	Psychological treatment for acute depression	Excluded studies in which all patients received the same psychological treatment and studies in which not all patients in a condition received psychological treatment.	NR	Depression was defined as meeting diagnostic criteria for major depressive disorder (MDD) or its equivalent in an earlier nosology (e.g., Research Diagnostic Criteria or Feighner criteria). We included studies that sampled patients who did not meet criteria for MDD only if outcomes were reported separately for those who did (since those were the patients included in our analyses).
Harerimana, 2019[77]	Study sample must have included adults age ≥65 years who are either clinically diagnosed with depression or self-reported depressive symptoms.	Studies that examined the use of telehealth for mental healthcare delivery. Telehealth in this review involved mental healthcare delivery using mobile applications, smart technologies, teleconferencing systems, Internet-based therapies, and Skype (videoconferencing) calls.	Control group conditions included patients on a waiting list and/or treatment as usual. However, studies where a control group was not included were considered if they met other eligibility criteria	NR	NR
Harper Shehadeh, 2016[78]	Studies where more than 75% of participants above a clinical cutoff for symptoms of unipolar	Studies that have a minimally-guided or unguided self-help program; 1 hour or less of face-to-face health	Any control condition, including placebo, treatment/care as usual, waitlist control, or active treatment	Studies where interventions were delivered in inpatient setting	Postintervention measures of symptoms of mental illness

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
	depression or anxiety including trauma-related disorders, irrespective of the clinical measure used; people culturally and linguistically different to those for which the intervention was originally designed	worker or trained layperson time or up to 90 minutes total telephone or email support, regardless of delivery mode; structured and active therapeutic modality (i.e., the intervention has clear theoretical underpinnings or an evidence base); must include methodology used (i.e., an observational or controlled study, process report, or a protocol)	comparison		
Holvast, 2017[79]	Adults age ≥60 years with depression	(a) Sample sizes ≥5 patients; (b) depression as the primary outcome; (c) a study population of adults age ≥60 years at the moment of inclusion (or there were adequately reported sub-analyses of adults age ≥60 years); (d) was conducted in a primary care or community setting; and (e) reported non-pharmacological treatments applicable in these settings.	NR	Limited to primary care or community settings	(1) Mean change, defined as the difference in depressive symptoms between baseline and followup measurement; (2) responders, defined as a ≥50% symptom reduction in the outcome measure between baseline and followup (unless stated otherwise); and (3) remission from depression at followup measurement. The definition of remission differed between studies.

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Huang, 2018[80]	The cohort of patients included women who gave birth to an infant in the past year, with formal diagnosis of PND or with the risk of PND.	CBT therapy interventions. Forms of CBT included internet-based therapy, telephone-based therapy, in-home therapy, and mindfulness-based cognitive behavioral therapy.	Usual care, home visiting, waitlist control, or other conventional treatment	NR	Mean depression scores, common depression score scale includes Edinburgh Postnatal Depression Scale (EPDS) and Beck Depression Inventory (BDI-II); improvement rates of PND after treatments were also extracted.
Karyotaki, 2017[81]	Adults (age >18 years) with elevated symptoms of depression based on any diagnosis or any self-report scale of depression	Self-guided iCBT	Control condition (usual care, waiting list, or attention control) were included.	NR	NR
Karyotaki, 2018a[82]	Adults with acute depression	Randomized trials in which the effects of a guided Internet-based interventions treatment were compared with either an active or inactive comparison group (waiting list, care-as-usual, attention placebo, other) in adults with acute depression (diagnosed based on either a clinical interview or cutoff scores on self-report questionnaires). Guidance could be provided by either a professional or a	An active or inactive comparison group (waiting list, care-as-usual, attention placebo, other treatment)	NR	Adults with acute depression: diagnosed based on either a clinical interview or cutoff scores on self-report questionnaires. Majority of the studies used either the CES-D or BDI-I; BDI-II as an outcome measure. Two studies used the PHQ-9 and the MADRS.

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
		paraprofessional			
Letourneau, 2017[83]	Women defined as depressed in the antenatal or postpartum period (i.e., within the first year). Depression must be measured by a valid assessment tool (e.g., Edinburgh Postnatal Depression Scale) or been diagnosed by a physician and could range from mild to severe symptoms.	All types of treatment interventions for women diagnosed with AD or PPD (e.g., interpersonal psychotherapy, cognitive behavioral therapy, peer support, or maternal-child interaction guidance)	Another intervention group, treatment as usual, or a control group	NR	Inclusion of parenting and/or child development and health outcomes (e.g., cognitive, language, behavioral, mental, and physical health domains)
Li, 2022[84]	Women who 1) were pregnant or postpartum (i.e., within 12 months post-delivery) and 2) had risk factors for perinatal depression, anxiety and/or stress at baseline	Only trials of interventions explicitly stating the use of CBT alone or CBT with a co-intervention (CBT-CI).	Control groups include no-intervention control, treatment as usual (TAU), enhanced TAU, waitlist, attention controls (e.g., standard parenting education), informational booklet about TAU, or active controls.	No restrictions	Short-term efficacy was defined as mean score changes in depression, or anxiety symptoms from baseline (i.e., preintervention assessment) to immediately post-intervention. Long-term efficacy was defined as mean score changes from baseline to the end of followup (~12 months).
Massoudi, 2019[85]	Adult patients (age ≥18 years) with depressive and/or anxiety symptoms or with a primary diagnosis of a	Guided or self-guided e-health interventions; offered in primary care	Active controls but not e-health, waitlist controls, or no intervention	Primary care only	NR

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
	depressive and/or anxiety disorder, excluding obsessive compulsive disorder or posttraumatic stress disorder				
Nair, 2018[86]	Perinatal, postnatal, pregnant women	Telemedicine intervention in perinatal women	Treatment as usual, waitlist, or comparator groups	Telemedicine	NR
Nieuwenhuijsen, 2020[87]	Adult (age >17 years) workers (employees or self-employed) diagnosed with depressive disorder fulfilling criteria of DSM-IV, ICD-10, or RDC for one of the following disorders: dysthymic disorder, minor depressive disorder, or major depressive disorder.	Healthcare interventions based on two mechanisms: one is improving conditions related to work, such as helping workers with depressive symptoms to overcome barriers that prevent them from working such as reducing work hours, changing tasks, light duty, graded work exposure addressing causes of depression at work such as a conflict, or supporting the worker in coping with the consequences of their depression in the workplace. This mechanism was called "work-directed interventions." The other mechanism was called "clinical interventions" and it was through	Any other intervention (no work-directed or clinical interventions), no intervention, or care as usual	Occupational health settings, primary care, or outpatient care settings.	Reduction in work disability was defined as a reduction in sickness absence and as enhancement in work functioning.

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
		improvement of depressive symptoms as is usual in treatment situations, assuming that the symptoms are the main barrier for not being at work. For clinical interventions, distinctions were made among the following treatment modalities: psychological or psychiatric treatment, antidepressants, a combination of these two, and other interventions such as improved care, exercise, and diet.			
Pineros-Leano, 2017[88]	Studies that had a sample of at least 50% Latino immigrant adults being treated in the US (mean age ≥18 years) or presented disaggregated results for this population and assessed depressive symptoms using a standardized measure	Studies that used a cognitive behavioral intervention to treat depressive symptoms	NR	NR	Included studies that assessed depressive symptoms using a standardized measure
Ponting, 2020[89]	Study participants had to be a) pregnant women, b) age ≥18 years, and c) residing in the US. Further, a majority of the	Psychological interventions were inclusive of manualized psychoeducational strategies, cognitive behavioral therapy,	NR	NR	Studies also had to measure depression and anxiety symptoms as an outcome using standardized depression and anxiety instruments

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
	sample (75% or more) had to identify as Latina/Hispanic or Black/African American	interpersonal psychotherapy, psychodynamic therapy, acceptance and commitment therapy, and mindfulness training delivered during the prenatal period via telephone, home, or clinic visits, or individual or group sessions by a health professional or lay person			(e.g., EPDS)
Rojas-Garcia, 2015[90]	Participants were socially disadvantaged patients with depressive disorders. The participants were judged to be socially disadvantaged when at least two thirds of them were characterized as having low-income and/or low-educational levels and/or unemployed. Depressive disorders had to be determined either according to 1) DSM and/or ICD-10 criteria for major or minor depression, or as ascertained by screening	Interventions were delivered via the healthcare system and target the patients (and not health professionals or health services organization)	Control groups had to receive usual care or enhanced usual care	Studies taking place in the primary, secondary or tertiary care setting	Studies had to include at least one measure of depressive disorders, which had to be determined either according to the DSM/ICD-10 as ascertained by previously described screening instruments.

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
	instruments for depressive disorders for which there is available empirical evidence supporting their psychometric properties in terms of reliability, validity and/or responsiveness (e.g., BDI or HDRS).				
Roman, 2020[91]	Mothers (age 18 years) in the postpartum period (first year after childbirth)	Internet CBT (therapist-supported via phone, email, or website)	Waitlist or usual care	NR	Self-evaluation scales for depression (EPDS; PHQ-9; BDI-II) and structured clinical interviews (Structured Clinical Interview for DSM Disorders – SCID-IV).
Thomas, 2018[92]	Older adults (age ≥55 years) with primary diagnosis of depression	CBT-based interventions for depression	Control condition (active and nonactive) or treatment comparison condition	NR	Determined by a diagnostic clinical interview and/or by meeting a level of depression severity above the cutoff scores on self-rated or clinician-rated depression scales.
Weaver, 2017[93]	Adults age >18 years; rural or remote population	(a) the sample or intervention delivery site was identified as rural or remote; (b) the intervention was a CBT-based program and included at least one core treatment element (e.g., behavioral	No requirement	NR	Clinical diagnosis, symptom measures, or clinical judgment

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
		activation, cognitive restructuring, exposure); (c) the primary aim of the intervention study was to reduce the symptoms or incidence of depression and/or anxiety disorders, and the primary outcome measure was symptoms or diagnosis of the targeted disorder; (d) study participants were adults; and (e) the study was published in a peer-reviewed, English-language journal.			
Weitz, 2018[94]	Adults with a primary diagnosis or elevated symptoms of depression established by a standardized diagnostic interview or a standardized clinician or self-report measure of depressive symptoms.	Psychotherapeutic treatment including at least 3 treatment sessions, in which either verbal communication between a therapist and client was central to the psychotherapy, or psychological treatment in book or internet format which clients work through individually supported by a therapist (by telephone or e-mail)	Control conditions (wait-list, pill placebo, care-as-usual, other)	NR	Required a continuous measure of anxiety (general symptoms)
Xiang, 2020[95]	Studies in older adults: in which all patients were age ≥50 years and their mean age was ≥60 years. Studies using	Intervention studies that tested the effectiveness of iCBT for depression or depressive symptoms. Studies that tested transdiagnostic iCBT	Active (treatment-as-usual or standard-of-care control condition such as face-to-face CBT) or non-active controls (waitlist or non-	NR	Studies that used self-reported or clinician-rated measures of depressive symptoms were both included.

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
	mixed-age samples were eligible only if the analyses were stratified by age groups so an effect size specific to older adults could be calculated. Participants were classified as having a depression concern if they had (1) a diagnosis of depression according to the Diagnostic and Statistical Manual of Mental Disorders, the International Classification of Diseases, or the Research Diagnostic Criteria, or (2) symptoms of depression on self-reported or clinician-administered standardized rating scales, or (3) difficulty with depression based on self-reported measures.	Interventions designed to treat core symptoms of anxiety and depression in mixed depression and anxiety samples were included if 80% or more of their samples had at least mild depressive symptoms or concerns of depression. The main component of the eligible interventions must have been delivered via websites (i.e., web-based) or dedicated apps on mobile devices or tablets.	treatment control)		
Zhang, 2019a[96]	NR	Study must have examined one of the four interventions targeted in this review, cognitive behavioral therapy,	NR	Study had to examine a primary care-based intervention as defined by the	Study had to report at least one depressive or anxiety outcome

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
		problem-solving therapy, motivational interviewing, or solution-focused brief therapy.		following criteria: (1) an intervention delivered in a primary care setting by a healthcare provider or through a technological platform or a combination of both, or (2) an intervention delivered outside a primary care setting by a healthcare provider or through a technological platform, or a combination of both, but directly connected with or prescribed by a primary care health care provider	
Zhang, 2019b[97]	NR	Studies targeting depressive and/or anxiety as primary outcomes. CBT needed to be provided inside a primary care setting by a health care provider, through a technological	NR	Studies had to be conducted in a primary care-based setting	NR

Appendix E Table 15. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
		platform, or via a combination of both, or (2) CBT delivered outside a primary care setting by a health care provider, through a technological platform, or via a combination of both, but directly connected with or prescribed by a primary care health care provider. All modalities of CBT studies (e.g., technology-assisted; in-person; individual; group) were included in the current study			

Abbreviations: BDI = Beck Depression Inventory; CAU = care as usual; CBT = cognitive behavioral therapy; CES-D = Center for Epidemiological Studies Depression Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; HAM-D = Hamilton Rating Scale for Depression; iCBT = internet cognitive behavioral therapy; ICD-9/10 = International Classification of Diseases-ninth/tenth edition; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; NR = not reported; PHQ = Patient Health Questionnaire; POM = Profile Of Mood States Questionnaire; QoL = quality of life; PND = postnatal depression; PPD = postpartum depression; RCT = randomized controlled trials; SLC = symptom checklist; sx = symptom; UC = usual care; US = United States; WL = waitlist.

Appendix E Table 16. Results for Depression Symptoms Severity From ESRs of Psychological Treatment for Depression (KQ4)

Author, Year	Intervention	Outcome	Population	Control	FUP, wks	k	N Analyzed	Pooled Risk	Est (95% CI)	I^2 (%)
Cuijpers, 2020[75]	Psychotherapy (any)	Main depression outcome	All participants	Any	Post-tx	385	NR	Hedges' g	-0.72 (-0.78 to -0.67)	81
Cuijpers, 2019a[73]	Psychotherapy (any)	HAMD	All participants	Any	NR	103	NR	Hedges' g	-0.86 (-0.97 to -0.75)	74
	Psychotherapy (any)	BDI	All participants	Any	NR	128	NR	Hedges' g	-0.87 (-0.98 to -0.77)	72
	Psychotherapy (any)	BDI-II	All participants	Any	NR	80	NR	Hedges' g	-0.68 (-0.80 to -0.57)	74
	Psychotherapy (any)	Main depression outcome	All participants	UC	NR	158	NR	Hedges' g	-0.61 (-0.70 to -0.52)	78
Cuijpers, 2020[75]	Psychotherapy (any)	Main depression outcome	All participants	UC	NR	165	NR	Hedges' g	-0.63 (-0.70 to -0.55)	80
	Psychotherapy (any)	Main depression outcome	All participants	WL	NR	157	NR	Hedges' g	-0.73 (-0.77 to -0.69)	75
	Psychotherapy (any)	Main depression outcome	All participants	Oth	NR	63	NR	Hedges' g	-0.57 (-0.70 to -0.43)	85
Zhang, 2019b[97]	Psychotherapy (any)	Main depression outcome	Primary care-based recruitment	Any	NR	59	113	Hedges' g	-0.42 (-0.56 to -0.29)	NR
Rojas-Garcia, 2015[90]	Psychotherapy (any)	Main depression outcome	Low SES	UC or EUC	Long-term	4	NR	SMD	-0.53 (-1.12 to 0.05)	86.4
	Psychotherapy (any)	Main depression outcome	Low SES	UC or EUC	Short-term	5	NR	SMD	-0.66 (-0.92 to -0.41)	36.7
Castro, 2020[69]	Psychotherapy, telephone-administered	Depression sx	All participants	UC or WL	NR	4	288	SMD	-0.85 (-1.56 to -0.15)	87
Massoudi, 2019[85]	Psychotherapy, e-health	Main depression	Primary care-based	Any	Long-term	9	2707	SMD	-0.22 (-0.35 to -0.09)	57

Appendix E Table 16. Results for Depression Symptoms Severity From ESRs of Psychological Treatment for Depression (KQ4)

Author, Year	Intervention	Outcome	Population	Control	FUP, wks	k	N Analyzed	Pooled Risk	Est (95% CI)	I^2 (%)
		outcome	recruitment							
	Psychotherapy, e-health	Depression sx	Primary care-based recruitment	Any	Short-term	11	2952	SMD	-0.19 (-0.31 to -0.06)	58
	Psychotherapy, e-health	Depression sx	Primary care-based recruitment	UC	Short-term	9	2241	SMD	-0.14 (-0.26 to -0.02)	39
	Psychotherapy, e-health	Depression sx	Primary care-based recruitment	UC	Long-term	3	561	SMD	-0.45 (-0.62 to -0.29)	0
Rojas-Garcia, 2015[90]	Counseling	Main depression outcome	Low SES	UC or EUC	Short-term	2	NR	SMD	-0.25 (-0.54 to 0.04)	0
	Counseling	Main depression outcome	Low SES	UC or EUC	Long-term	3	NR	SMD	-0.41 (-0.70 to -0.12)	0
Cuijpers, 2020[75]	CBT	Main depression outcome	All participants	Any	Post-tx	205	NR	Hedges' g	-0.73 (-0.80 to -0.65)	80
Li, 2022[84]	CBT	Depression sx	Perinatal	Any	Post-tx	37	4374	SMD	-0.59 (-0.75 to -0.42)	84
	CBT	Depression sx	Perinatal	Any	Long-term (~12m)	54	5393	SMD	-0.69 (-0.83 to -0.55)	81
Zhang, 2019a[96]	CBT	Main depression outcome	Primary care-based recruitment	Any	NR	51	NR	Hedges' g	-0.42 (-0.60 to -0.25)	NR
Thomas, 2018[92]	CBT	Depression sx	Older adults	Any	4-13	12	NR	Hedges' g	-0.60 (-1.00 to -0.19)	78
	CBT	Depression sx	Older adults	Any	43-52	5	NR	Hedges' g	-0.14 (-0.42 to 0.14)	44
	CBT	Depression sx	Older adults	Any	26-39	10	NR	Hedges' g	-0.49 (-0.81 to -0.17)	72
	CBT	Depression sx	Older adults	Any	Post-tx	52	2,925	Hedges' g	-0.63 (-0.76 to -0.49)	66

Appendix E Table 16. Results for Depression Symptoms Severity From ESRs of Psychological Treatment for Depression (KQ4)

Author, Year	Intervention	Outcome	Population	Control	FUP, wks	k	N Analyzed	Pooled Risk	Est (95% CI)	I^2 (%)
Holvast, 2017[79]	CBT	Main depression outcome	Older, PC	Any	26	4	445	SMD	-0.21 (-0.40 to -0.03)	0
	CBT	Main depression outcome	Older, PC	Any	Short-term	4	274	SMD	-0.16 (-0.34 to 0.02)	0
Xiang, 2020[95]	iCBT	Main depression outcome	Older adults	Any	NR	4	214	SMD	-1.18 (-1.73 to -0.63)	68
Roman, 2020[91]	iCBT	Depression sx	Postpartum mothers	UC or WL	10-69	6	635	SMD	-0.55 (-0.76 to -0.34)	25
Karyotaki, 2017[81]	Self-guided, iCBT	Depression sx	All participants (Traditional MA)	Any	6-16	13	NR	Hedges' g	-0.33 (-0.46 to -0.19)	71
Cuijpers, 2020[75]	IPT	Main depression outcome	All participants	Any	Post-tx	27	NR	Hedges' g	-0.60 (-0.86 to -0.34)	87
	PST	Main depression outcome	All participants	Any	Post-tx	30	NR	Hedges' g	-0.75 (-0.97 to -0.53)	87
	BAT	Main depression outcome	All participants	Any	Post-tx	21	NR	Hedges' g	-1.05 (-1.30 to -0.80)	77
	3rd wave therapy	Main depression outcome	All participants	Any	Post-tx	19	NR	Hedges' g	-0.85 (-1.07 to -0.63)	75
	Psychodynamic	Main depression outcome	All participants	Any	Post-tx	12	NR	Hedges' g	-0.39 (-0.62 to -0.16)	70
	Non-directive supportive	Main depression outcome	All participants	Any	Post-tx	19	NR	Hedges' g	-0.58 (-0.75 to -0.42)	45
	Life review	Main depression	All participants	Any	Post-tx	14	NR	Hedges' g	-1.10 (-1.51 to -0.68)	89

Appendix E Table 16. Results for Depression Symptoms Severity From ESRs of Psychological Treatment for Depression (KQ4)

Author, Year	Intervention	Outcome	Population	Control	FUP, wks	k	N Analyzed	Pooled Risk	Est (95% CI)	I^2 (%)
		outcome								
	Other (psychotherapy)	Main depression outcome	All participants	Any	Post-tx	52	NR	Hedges' g	-0.70 (-0.84 to -0.56)	78
Rojas-Garcia, 2015[90]	Combined (Psych+Pharm)	Main depression outcome	Low SES	UC or EUC	Short-term	3	NR	SMD	-0.68 (-0.97 to -0.40)	55.0
	Combined (Psych+Pharm)	Main depression outcome	Low SES	UC or EUC	Long-term	3	NR	SMD	-0.47 (-0.97 to 0.03)	85.0

Abbreviations: BAT = behavioral activation therapy; BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CI = confidence interval; Est = estimated; EUC = enhanced usual care; k = number of studies; HAM-D = Hamilton Rating Scale for Depression; iCBT = internet cognitive behavioral therapy; IPT = interpersonal therapy; NR = not reported; Oth = other; PST = problem solving therapy; SES = socioeconomic status; SMD = standardized mean difference; sx = symptoms; Post-tx = post treatment; UC = usual care.

Appendix E Table 17. Results of Analyses From ESRs Examining Effect Modification of Depression Symptom Severity for Psychological Treatment of Depression (KQ4)

Author, Year	Effect mod category	Population	Intervention	Control	k	N Analyzed	Pooled risk	Est (95% CI)	I^2 (%)	Effect modification results
Cuijpers, 2018a[72]	Age	General adults	Psychotherapy (any)	Any	275	NR	Hedges' g	-0.68 (-0.74 to -0.63)	72	Effects among students > general and older adult populations
	Age	Older adults	Psychotherapy (any)	Any	39	NR	Hedges' g	-0.78 (-0.98 to -0.59)	85	Effects among students > general and older adult populations
	Age	Students	Psychotherapy (any)	Any	18	NR	Hedges' g	-1.15 (-1.39 to -0.91)	42	Effects among students > general and older adult populations
	Comorbidities	Comorbid medical condition	Psychotherapy (any)	Any	48	NR	Hedges' g	-0.57 (-0.69 to -0.44)	71	Smaller effect sizes in studies that are limited to people with medical comorbidities
	Comorbidities	Not limited to comorbid medical condition	Psychotherapy (any)	Any	284	NR	Hedges' g	-0.74 (-0.80 to -0.68)	75	Smaller effect sizes in studies that are limited to people with medical comorbidities
	Control type	All participants	Psychotherapy (any)	Pill placebo	11	NR	Hedges' g	-0.36 (-0.55 to -0.18)	52	Smaller effect in studies with pill placebo than other types of controls
Cuijpers, 2019b[74]	Control type	All participants	Psychotherapy (any)	UC, PC	37	NR	Hedges' g	-0.46 (-0.60 to -0.31)	72	No effect modification by usual care category
	Control type	All participants	Psychotherapy (any)	UC, US PC	5	NR	Hedges' g	-0.95 (-1.74 to -0.16)	87	Larger effects in US-based primary care compared to UK- or NDL-based

Appendix E Table 17. Results of Analyses From ESRs Examining Effect Modification of Depression Symptom Severity for Psychological Treatment of Depression (KQ4)

Author, Year	Effect mod category	Population	Intervention	Control	k	N Analyzed	Pooled risk	Est (95% CI)	I^2 (%)	Effect modification results
										primary care
	Control type	All participants	Psychotherapy (any)	UC, gen med	38	NR	Hedges' g	-0.58 (-0.74 to -0.42)	74	No effect modification by usual care category
	Control type	All participants	Psychotherapy (any)	UC, perinatal	25	NR	Hedges' g	-0.69 (-0.96 to -0.41)	79	No effect modification by usual care category
	Control type	All participants	Psychotherapy (any)	UC, MH	29	NR	Hedges' g	-0.68 (-0.99 to -0.36)	80	No effect modification by usual care category
	Control type	All participants	Psychotherapy (any)	UC, US MH	7	NR	Hedges' g	-0.21 (-0.33 to -0.08)	0	Smaller effects in studies with usual US-based specialty mental health control group (vs. NDL)
	Control type	All participants	Psychotherapy (any)	No tx	29	NR	Hedges' g	-0.73 (-0.94 to -0.51)	80	No effect modification by usual care category
Thomas, 2018[92]	Control type	Older adults	CBT	UC or WL	24	NR	Hedges' g	-0.92 (-1.12 to -0.72)	46	larger treatment effect than active (e.g., education group) controls (g= -0.37; 95% CI: -0.52 to -0.23; p<0.001).
Cuijpers, 2018a[72]	Depression criteria	Any mood disorder	Psychotherapy (any)	Any	70	NR	Hedges' g	-0.83 (-0.99 to -0.68)	84	No differences between studies based on type of depression

Appendix E Table 17. Results of Analyses From ESRs Examining Effect Modification of Depression Symptom Severity for Psychological Treatment of Depression (KQ4)

Author, Year	Effect mod category	Population	Intervention	Control	k	N Analyzed	Pooled risk	Est (95% CI)	I^2 (%)	Effect modification results
										inclusion criteria
	Depression criteria	Chronic depression	Psychotherapy (any)	Any	7	NR	Hedges' g	-0.70 (-1.14 to -0.26)	75	No differences between studies based on type of depression inclusion criteria
	Depression criteria	Cut-off score	Psychotherapy (any)	Any	147	NR	Hedges' g	-0.69 (-0.77 to -0.62)	69	No differences between studies based on type of depression inclusion criteria
	Depression criteria	MDD diagnosis	Psychotherapy (any)	Any	97	NR	Hedges' g	-0.68 (-0.78 to -0.59)	69	No differences between studies based on type of depression inclusion criteria
Cuijpers, 2018a[72] continued	Depression criteria	Subthreshold depression	Psychotherapy (any)	Any	11	NR	Hedges' g	-0.61 (-0.88 to -0.34)	82	No differences between studies based on type of depression inclusion criteria
	Format	All participants	Psychotherapy, individual	Any	113	NR	Hedges' g	-0.79 (-0.90 to -0.68)	81	Smaller effect in studies with other/mixed format (vs individual, group, or guided self-help)
	Format	All participants	Psychotherapy, individual	Any	145	NR	Hedges' g	-0.71 (-0.80 to -0.63)	73	Smaller effect in studies with other/mixed format (vs individual, group, or guided self-help)
	Format	All	Psychotherapy,	Any	17	NR	Hedges'	-0.49	46	Smaller effect in

Appendix E Table 17. Results of Analyses From ESRs Examining Effect Modification of Depression Symptom Severity for Psychological Treatment of Depression (KQ4)

Author, Year	Effect mod category	Population	Intervention	Control	k	N Analyzed	Pooled risk	Est (95% CI)	I^2 (%)	Effect modification results
		participants	other/mixed format				g	(-0.64 to -0.35)		studies with other/mixed format (vs individual, group, or guided self-help)
	Format	All participants	Guided self-help (any format)	Any	57	NR	Hedges' g	-0.67 (-0.77 to -0.58)	60	Smaller effect in studies with other/mixed format (vs individual, group, or guided self-help)
Cuijpers, 2018a[72] continued	Gender	Gender men and women	Psychotherapy (any)	Any	270	NR	Hedges' g	-0.73 (-0.80 to -0.67)	76	No differences between women only studies and those that include men and women.
	Gender	Women only	Psychotherapy (any)	Any	62	NR	Hedges' g	-0.64 (-0.75 to -0.54)	70	No differences between women only studies and those that include men and women.
Cuijpers, 2017[71]	No. sessions	All participants	Psychotherapy, 4-6 invididual sessions	Any	23	NR	Hedges' g	-0.47 (-0.65 to -0.30)	45	No effect modification by number of sessions (4 levels, ranging 4-24)
	No. sessions	All participants	Psychotherapy, 7-10 individual sessions	Any	27	NR	Hedges' g	-0.58 (-0.74 to -0.42)	69	No effect modification by number of sessions (4 levels, ranging 4-24)
	No. sessions	All participants	Psychotherapy, 12-16 individual sessions	Any	22	NR	Hedges' g	-0.68 (-0.85 to	57	No effect modification by number of sessions

Appendix E Table 17. Results of Analyses From ESRs Examining Effect Modification of Depression Symptom Severity for Psychological Treatment of Depression (KQ4)

Author, Year	Effect mod category	Population	Intervention	Control	k	N Analyzed	Pooled risk	Est (95% CI)	I^2 (%)	Effect modification results
								-0.50)		(4 levels, ranging 4-24)
	No. sessions	All participants	Psychotherapy, 18-24 individual sessions	Any	20	NR	Hedges' g	-0.61 (-0.81 to -0.41)	42	No effect modification by number of sessions (4 levels, ranging 4-24)
Cuijpers, 2018a[72]	Perinatal status	Not limited to perinatal	Psychotherapy (any)	Any	296	NR	Hedges' g	-0.74 (-0.80 to -0.68)	76	Smaller effect sizes in studies that are limited to perinatal patients
	Perinatal status	Perinatal	Psychotherapy (any)	Any	36	NR	Hedges' g	-0.59 (-0.70 to -0.48)	60	Smaller effect sizes in studies that are limited to perinatal patients
Driessen, 2015[76]	Publication bias	All participants (Unpublished studies)	Psychotherapy (any)	Any	6	NR	Hedges' g	-0.20 (-0.51 to 0.11)	4	NR
	Publication bias	All participants (Published + Unpublished)	Psychotherapy (any)	Any	26	NR	Hedges' g	-0.39 (-0.70 to -0.08)	50	Among comparisons to control conditions, adding unpublished studies (identified via NIH grant database) to published studies reduced the psychotherapy effect size point estimate by 25%.
	Publication bias	All participants (Published	Psychotherapy (any)	Any	20	NR	Hedges' g	-0.52 (-0.68 to	51	NR

Appendix E Table 17. Results of Analyses From ESRs Examining Effect Modification of Depression Symptom Severity for Psychological Treatment of Depression (KQ4)

Author, Year	Effect mod category	Population	Intervention	Control	k	N Analyzed	Pooled risk	Est (95% CI)	I^2 (%)	Effect modification results
		studies)						-0.37)		
Cuijpers, 2018a[72]	Race or ethnicity	Not specific race or ethnic	Psychotherapy (any)	Any	319	NR	Hedges' g	-0.72 (-0.77 to -0.66)	74	No differences between studies limited to race or ethnic "minority" populations vs not limited
	Race or ethnicity	Specific race or ethnic	Psychotherapy (any)	Any	13	NR	Hedges' g	-0.63 (-0.89 to -0.36)	73	No differences between studies limited to race or ethnic "minority" populations vs not limited
	Recruitment setting	Community-based recruitment	Psychotherapy (any)	Any	154	NR	Hedges' g	-0.67 (-0.73 to -0.61)	46	No effect modification by recruitment setting
	Recruitment setting	Other outpatient recruitment	Psychotherapy (any)	Any	39	NR	Hedges' g	-0.78 (-0.93 to -0.64)	52	No effect modification by recruitment setting
	Recruitment setting	Other recruitment	Psychotherapy (any)	Any	94	NR	Hedges' g	-0.59 (-0.68 to -0.50)	75	No effect modification by recruitment setting
	Recruitment setting	Primary care-based recruitment	Psychotherapy (any)	Any	30	NR	Hedges' g	-0.40 (-0.51 to -0.29)	49	No effect modification by recruitment setting
Cuijpers, 2019b[74]	See narrative	All participants	Psychotherapy (any)	UC, US perintal	3	NR	Hedges' g	-0.39 (-2.43 to 1.64)	87	No effect modification by country of perinatal care (US, UK, China, Australia)

Appendix E Table 17. Results of Analyses From ESRs Examining Effect Modification of Depression Symptom Severity for Psychological Treatment of Depression (KQ4)

Author, Year	Effect mod category	Population	Intervention	Control	k	N Analyzed	Pooled risk	Est (95% CI)	I^2 (%)	Effect modification results
Cuijpers, 2017[71]	Sessions/wk	All participants	Psychotherapy,	Any	10	NR	Hedges' g	-0.44 (-0.69 to -0.19)	64	Larger effects with greater sessions/week, controlling for total number of sessions
	Sessions/wk	All participants	Psychotherapy, 1 session/wk	Any	46	NR	Hedges' g	-0.58 (-0.70 to -0.46)	53	Larger effects with greater sessions/week, controlling for total number of sessions
	Sessions/wk	All participants	Psychotherapy, >1 session/wk	Any	22	NR	Hedges' g	-0.71 (-0.91 to -0.52)	53	Larger effects with greater sessions/week, controlling for total number of sessions

Abbreviations: BAT = behavioral activation therapy; BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CI = confidence interval; Est = estimated; EUC = enhanced usual care; k = number of studies; HAM-D = Hamilton Rating Scale for Depression; iCBT = internet cognitive behavioral therapy; IPT = interpersonal therapy; NR = not reported; Oth = other; PST = problem solving therapy; SES = socioeconomic status; SMD = standardized mean difference; sx = symptoms; Post-tx = post treatment; wk = week(s); UC = usual care.

Appendix E Table 18. Results From Narrative Syntheses From ESRs of Psychological Treatment of Depression (KQ4)

Author, Year	Population	Outcome Category	Outcome	Behavioral Intv	Intervention	Control	Findings
Holvast, 2017[79]	Older adults	Depression symptoms	Main depression outcome	Psychological	Bibliotherapy	Any	4 RCTs showed that bibliotherapy was effective at reducing depressive symptoms at 4 weeks' followup compared with remaining on a WL or being given a control form of bibliotherapy
Harerimana, 2019[77]	Older adults	Depression symptoms	Main depression outcome	E-interventions	Psychotherapy, telehealth (phone, video)	Any	Telehealth for mental health care among older adults with depressive symptoms demonstrated a positive impact, including reduced emergency visit and hospitalizations, reduced depressive symptoms, and improved cognitive functioning. (k=9, no pooling)
Aherne, 2017[68]	Moderate-level depression	Depression symptoms	Main depression outcome	Psychological	Psychotherapy (any)	Any	4 studies showed that CBT alone (k=3) or when combined with another form of psychotherapy (k=1) was effective in reducing moderate depressive symptoms; no pooling.
Pineros-Leano, 2017[88]	Latinx	Depression symptoms	Main depression outcome	CBT-specific	CBT	Oth	9 of 11 included RCTs (k=5) and pre-post/post-only (k=6) studies showed a reduction in depressive symptoms, however no apparent difference from usual care/comparison groups. (No pooled results)
Holvast, 2017[79]	Older adults	Depression symptoms	Main depression outcome	Psychological	Life review	Any	3 RCTs showed that Life Review found a positive effect on depressive symptoms from 2 to 8 weeks' followup.
	Older adults	Depression	Main	Psychological	PST	Any	3 RCTs showed that individually

Appendix E Table 18. Results From Narrative Syntheses From ESRs of Psychological Treatment of Depression (KQ4)

Author, Year	Population	Outcome Category	Outcome	Behavioral Intv	Intervention	Control	Findings
		symptoms	depression outcome				delivered PST reduced depressive symptoms.
Collado, 2016[70]	Latinx	Depression symptoms	Main depression outcome	Psychological	Psychotherapy (any)	Any	Among Latino populations, CBT generally showed greater improvement than usual care (k=18); they found "growing support" for PST (k=4) and IPT (k=4); the strongest support for IPT was for perinatal depression. (No pooled results)
Ponting, 2020[89]	Perinatal Black and Latina	Depression symptoms	Main depression outcome	Psychological	Psychotherapy (any)	Any	CBT: 1 of 4 included RCTs found statistically significant group differences. IPT: 1 of 4 included RCTs found statistically significant group differences. (No pooled results)
Weaver, 2017[93]	Rural	Depression symptoms	Main depression outcome	CBT-specific	Psychotherapy (any)	Any	Five of the 6 studies testing the effect of CBT for depression and 2 of the 3 studies for depression and anxiety found a statistically significant decrease in symptoms compared to controls. Where reported, Cohen's d effect sizes ranged from 0.03 to 2.69, suggesting variability in the effect of CBT across studies. However, the majority of studies reporting Cohen's d had effect sizes in the medium to large range.
Letourneau, 2017[83]	Perinatal	Family functioning	Mother-child interaction	Counseling	Psychotherapy (any)	Any	For AD, IPT, CBT, and massage produced large effects on parenting (e.g., adjustment and attention toward infant) and child development (e.g., behavior).

Appendix E Table 18. Results From Narrative Syntheses From ESRs of Psychological Treatment of Depression (KQ4)

Author, Year	Population	Outcome Category	Outcome	Behavioral Intv	Intervention	Control	Findings
							For PPD, maternal-child interaction guidance and psychotherapeutic group support produced large effects on parenting (e.g., sense of competence) and child development (e.g., cortisol). However, meta-analysis revealed nonsignificant effects of IPT on maternal-child attachment and CBT on parenting stress (pooled SMD=0.15 [95% CI, -0.01 to 0.31] p=0.06, k=6). Promising findings exist for IPT, CBT, maternal-child interaction guidance, massage, and psychotherapeutic group support for specific parenting and/or child development outcomes
Jonsson, 2016[98]	All participants	Adverse events	Adverse events	Psychological	Psychotherapy (any)	Any	Safety data were not reported in any included trials
Cuijpers, 2018a[72]	All participants	Depression symptoms	Main depression outcome	Psychological	Psychotherapy (any)	Any	According to Duval and Tweedie's trim and fill procedure, there was considerable publication bias, with 81 missing studies and an adjusted effect size of g = -0.50 (95% CI, -0.56 to -0.44; NNT = 6.14), vs. -0.71 (95% CI, -0.77 to -0.66) in the main analysis. When limited to the studies with low risk of bias, we still found significant publication bias, with 19 missing studies and an

Appendix E Table 18. Results From Narrative Syntheses From ESRs of Psychological Treatment of Depression (KQ4)

Author, Year	Population	Outcome Category	Outcome	Behavioral Intv	Intervention	Control	Findings
							adjusted effect size of g = -0.37 (95% CI, -0.44 to -0.31]; NNT = 8.64).
Thomas, 2018[92]	Older adults	Depression symptoms	Depression sx	CBT-specific	CBT	Any	Examined effect modification for specific depressive diagnosis, age category, allowed use of concurrent pharmacotherapy, recruitment (clinical, community, both), type of CBT, type of outcome measure, session format (individual, group, self-help), number of sessions, and intention-to-treat vs. completers only analysis. All NSD except (a) smaller and NSD effect for behavioral activation compared with other types of CBT (k=3), and (b) larger effect for completers only analysis, but both analysis types showed a statistically significant benefit.
Karyotaki, 2017[81]	All participants	Depression symptoms	Depression sx	E-interventions	Self-guided, iCBT	Any	Examined effect modification by gender, age, education level, in a relationship (vs. not), employment status, comorbid anxiety, baseline depression severity, presence of previous depression episodes, antidepressant use, problematic alcohol use. All NSD for both symptom level and response.
Karyotaki, 2018a[82]	All participants	Depression remission	Depression remission	E-interventions	Guided, internet-based intv	Any	Examined effect modification for gender, age, ethnicity (native born vs. not), education level, in a relationship (vs. not),

Appendix E Table 18. Results From Narrative Syntheses From ESRs of Psychological Treatment of Depression (KQ4)

Author, Year	Population	Outcome Category	Outcome	Behavioral Intv	Intervention	Control	Findings
							employment status, comorbid anxiety, baseline depression severity, presence of previous depression episodes, antidepressant use, and problematic alcohol use. All NSD except larger effect associated with older age, being native born, and higher baseline severity.
Cuijpers, 2017[71]	All participants	Depression response	Depression response	Psychological	Psychotherapy (any)	Any	No statistically significant association between effect size and total contact time, number of sessions, or duration of the therapy after controlling for other study characteristics. However, there was a larger effect with more sessions/wk.
Karyotaki, 2017[81]	All participants	Depression response	Depression response	E-interventions	Self-guided, iCBT	Any	No effect modification by age, sex, education level, relationship status, employment status, comorbid anxiety, or baseline depression severity.

Abbreviations: AD = antenatal depression; CBT = cognitive behavioral therapy; CI = confidence interval; iCBT = internet cognitive behavioral therapy; IPT = interpersonal therapy; intv = intervention; NNT = number needed to treat; NSD = no significant difference; PPD = postpartum depression; PST = problem solving therapy; RCT = randomized controlled trial; SMD = standardized mean difference; WL = waitlist.

Appendix E Table 19. Results for Remission and Response to Treatment From ESRs of Psychological Treatment for Depression (KQ4)

Author, Year	Intervention	Outcome	Population	Control	Followup	k	N analyzed	Effect	ES (95% CI)	I^2 (%)
Huang, 2018[80]	CBT	Depression remission	Postpartum patients	Any	FUP (NOS)	9	1,558	OR	2.00 (1.61 to 2.48)	0
	CBT	Depression remission	Postpartum patients	Any	Post-tx	4	590	OR	6.57 (1.84 to 23.48)	60
Karyotaki, 2018a[82]	Guided, internet-based intv	Depression remission	All participants	Any	5-13	26	4,867	OR	2.41 (2.07 to 2.79)	NR
Cuijpers, 2017[71]	Psychotherapy (any)	Depression response	All participants	Any	27+	55	NR	OR	1.92 (1.60 to 2.31)	65
	Psychotherapy (any)	Depression response	All participants	Any	53+	11	NR	OR	1.59 (1.14 to 2.21)	55
Karyotaki, 2017[81]	Self-guided, iCBT	Depression response	All participants	Any	Post-tx	13	3,795	Beta coefficient	0.53 (NR)	NR
Karyotaki, 2018a[82]	Guided, internet-based intv	Depression response	All participants	Any	5-13	26	4,867	OR	2.49 (2.17 to 2.85)	NR

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; ES = effect size; FUP = followup; iCBT = internet cognitive behavioral therapy; intv = intervention; NOS = not otherwise specified; NR = not reported; OR = odds ratio; tx = treatment.

Appendix E Table 20. Pooled Standardized Mean Differences Between Groups for Health Outcomes Other Than Depression in ESRs of Psychological Treatment of Depression (KQ4)

Author, Year	Intervention	Outcome	Population	Control	Followup	k	N analyzed	Effect	ES (95% CI)	I^2 (%)
Weitz, 2018[94]	Psychotherapy (any)	Anxiety Sx	All participants	Any	NR	62	NR	Hedges' g	-0.52 (-0.60 to -0.44)	55
Huang, 2018[80]	CBT	Anxiety Sx	Postpartum mothers	Any	Long-term	2	72	MD	-0.81 (-3.22 to 1.59)	0
	CBT	Anxiety Sx	Postpartum mothers	Any	Short-term	2	72	MD	-4.64 (-12.62 to 3.33)	84
Cuijpers, 2017[71]	Psychotherapy (any)	Suicidality	All participants	Any	NR	4	NR	Hedges' g	-0.12 (-0.44 to 0.20)	31
	Psychotherapy (any)	Hopelessness	All participants	Any	NR	18	NR	Hedges' g	-1.10 (-1.48 to -0.72)	77
	Psychotherapy (any)	QoL	All participants	Any	NR	31	NR	Hedges' g	0.33 (0.24 to 0.42)	21
	Psychotherapy (any)	Social Fx	All participants	Any	NR	39	NR	Hedges' g	0.46 (0.32 to 0.60)	71
	Psychotherapy (any)	Parental Fx	All participants	Any	NR	5	NR	Hedges' g	0.67 (0.30 to 1.04)	51
	Psychotherapy (any)	Mother-child interaction	All participants	Any	NR	8	NR	Hedges' g	0.35 (0.17 to 0.52)	0
	Psychotherapy (any)	MH in children	All participants	Any	NR	7	NR	Hedges' g	0.40 (0.22 to 0.59)	1
Nieuwenhuijsen, 2020[87]	ACT	Occupational Fx	All participants	UC	13	1	58	SMD	0.05 (-0.46 to 0.57)	NR
	Psychotherapy (any)	Sickness absence	All participants	UC	9-52	9	1649	SMD	-0.15 (-0.28 to -0.03)	NR

Abbreviations: ACT = acceptance and commitment therapy; CBT = cognitive behavioral therapy; CI = confidence interval; ES = effect size; Fx = functioning; MD = mean difference; MH = mental health; NR = not reported; QoL = quality of life; SMD = standardized mean difference; UC = usual care.

Appendix E Table 21. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Arroll, 2016[99]	Primary care studies that examined the outcomes of antidepressant treatment of patients with depression where there was a placebo comparison group. "Primary care studies" were defined as ≥50% of the study sample being subjects who have been recruited from primary care settings. "Patients with depression" were defined as subjects diagnosed with depression by a primary care clinician or by diagnostic inventory or criteria	Any class of antidepressant medication. The treating clinician could be from primary or secondary care, as we were interested in the drug/placebo difference and any non-drug skill would apply equally to all arms of the trials	Placebo	NR	Response or remission to treatment for dichotomous outcomes, and the Hamilton Depression Rating Scale (HAM-D) or the Montgomery Asberg Rating Scale (MADRS) for continuous outcomes.
Baune, 2018[100]	Adult patients age ≥18 years with major depressive disorder	Pharmacological interventions: SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), SNRIs (desvenlafaxine, duloxetine, venlafaxine, milnacipran, levomilnacipran), TCAs (desipramine, imipramine, clomipramine, nortriptyline, tianeptine, dothiepin, opipramol, trimipramine, lofepramine, dibenzepin, amitriptyline, protriptyline, doxepin, melitracen, butriptyline, dimetacrine, quinupramine), TeCA	Any of the included interventions; Placebo/best supportive care	NR	Studies evaluating the effect of listed interventions on cognition in MDD patients were included. Studies that assess the impact of cognitive dysfunction on patient's daily functioning, work productivity, and

Appendix E Table 21. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
		(mirtazapine, maprotiline, mianserin, amoxapine), MAOI (moclobemide, isocarboxazid, tranylcypromine, phenelzine, toloxatone); Nonpharmacological interventions: Cognitive therapy/remediation therapy, Exercise therapy; Other antidepressants: bupropion, reboxetine, viloxazine, trazodone, vortioxetine, etoperidone, nefazodone, bifemelane, agomelatine, vilazodone; Alternative therapy: Diet therapy, S-adenosylmethionine, vitamins, omega 3 fatty acid, tryptophan, 5-hydroxytryptophan, hypericum perforatum			quality of life were also of interest in the review
Cipriani, 2018[101]	Adults (age ≥18 years) with a primary diagnosis of MDD according to standard diagnostic criteria (Feighner criteria, Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV, DSM-5, and ICD-10)	RCTs comparing antidepressants with placebo or another active antidepressant as oral monotherapy for the acute treatment of adults with primary diagnosis of MDD. Additionally, included all second-generation antidepressants approved by the regulatory agencies in the US, Europe, or Japan: agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine, vilazodone, and vortioxetine; two tricyclics (amitriptyline and clomipramine); trazodone and nefazodone.	Placebo or another active antidepressant as oral monotherapy	NR	Efficacy (response rate measured by the total number of patients who had a reduction of ≥50% of the total score on a standardized observer-rating scale for depression) and acceptability (treatment discontinuation measured by the proportion of patients who withdrew for any reason). When depressive symptoms had been

Appendix E Table 21. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
		Additionally, included trials that allowed rescue medications so long as they were equally provided among the randomized groups			measured with more than one standardized rating scale, we used a predefined hierarchy, based on psychometric properties and consistency of use. 8-week outcomes were selected if available, or the closest to 8 weeks (within 4-12 weeks).
Cuijpers, 2015[102]	Adults with depressive disorder	Combined treatment consisting of a psychological and a pharmacological intervention	A pill placebo only; pharmacotherapy only; psychotherapy only; or a psychotherapy plus pill placebo (only included placebo comparison)	NR	Effect sizes were standardized mean differences (Hedge's g) from only instruments that explicitly measured symptoms of depression (e.g., HAM-D, BDI). Thresholds were not reported.
Krause, 2019[103]	Age ≥65 years	Any pharmacologic or non-pharmacologic intervention (included only for pharmacologic evidence; non-pharmacologic superseded by other reviews)	NR	Excluded studies from mainland China; studies before 1990	At least 50% reduction on the HAM-D, MADRS, BDI, or any other validated depression scale; or "much or very much improved" (score 1 or 2) on CGI improvement; number of

Appendix E Table 21. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
					participants in remission; depressive symptoms at endpoint/mean reduction of depressive symptoms from baseline to endpoint; dropouts owing to any reason (all-cause discontinuation), dropouts owing to inefficacy of treatment, and dropouts due to adverse events. Further efficacy outcomes we analyzed were quality of life and social functioning
Lee, 2018[104]	Adult subjects with MDD as defined by the DSM (any edition)	Interventions were pharmacological antidepressants as classified by the Neuroscience-Based Nomenclature	Placebo or active comparator	NR	Work functioning and/or absence assessed using a standardized metric and reported as a study outcome.
Lisinski, 2020[105]	Patient-level data for 15 drug company-sponsored, placebo-controlled clinical trials regarding the treatment of	Duloxetine	Placebo	NR	Studies using the HDRS-17 for assessment of efficacy obtained from the Clinical Study Data Request

Appendix E Table 21. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
	depression in adults with duloxetine				(CSDR) website.
Rabinowitz, 2016[106]	NR	Patient- and trial-level data from 34 randomized placebo-controlled trials. Selected RCTs (1987-2007) of citalopram, duloxetine, escitalopram, quetiapine and sertraline from the NEWMEDS registry. This included all acute placebo-controlled trials of major depressive disorder in adult populations sponsored or owned by Pfizer (12 studies; active: n = 2,455, placebo: n = 888), Lilly (11 studies; active: n = 2,425, placebo: n = 1,134), AstraZeneca (4 studies; active: n = 1,021, placebo: n = 524) and Lundbeck (7 studies; active: n = 1,509, placebo n = 781) on these five compounds.	Placebo	NR	In three studies the Hamilton Rating Scale for Depression (HRSD) was estimated based on the Montgomery–Asberg Depression Rating Scale (MADRS) using equipercentile linking, which gives an equivalent score of one measure on the other measure. It was done using data from 16 studies that included both measures
Rojas-Garcia, 2015[90]	Participants were socially disadvantaged patients with depressive disorders. The participants were judged to be socially disadvantaged when at least two thirds of them were characterized as having low income and/or low educational levels	Interventions were delivered via the healthcare system and target the patients (and not health professionals or health services organization)	Control groups had to receive usual care or enhanced usual care	Studies taking place in the primary, secondary, or tertiary care setting	Studies had to include at least one measure of depressive disorders, which had to be determined either according to the DSM/ICD-10 as ascertained by previously described screening instruments.

Appendix E Table 21. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
	and/or unemployed. Depressive disorders had to be determined either according to 1) DSM and/or ICD-10 criteria for major or minor depression, or as ascertained by screening instruments for depressive disorders for which there is available empirical evidence supporting their psychometric properties in terms of reliability, validity and/or responsiveness (e.g., BDI or HDRS).				
Viswanathan, 2021[107]	For tx: Studies in women who are pregnant or postpartum with new or preexisting diagnosis of anxiety, depression, bipolar disorder, or schizophrenia. For tx harms: Reproductive-aged women (15-44 years old during preconception [≤12	All US FDA-approved drugs for mental health disorders and off-label drugs used for mental health disorders were eligible	Placebo or no tx, or other pharmacologic interventions	NR	NR

Appendix E Table 21. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
	weeks before pregnancy], pregnancy, and postpartum [through 1 year]) with any mental health disorder (new or preexisting)				

Abbreviations: BDI = Beck Depression Inventory; CGI = Clinical Global Impressions scale; DSM = Diagnostic and Statiscal Manual; HAM-D = Hamilton Depression Rating Scale; ICD = International Classification of Disease; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; NEWMEDS = Novel methods leading to new medications in depression and schizophrenia; NR = not reported; RCT = randomized controlled trial; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA or TeCA = tricyclic antidepressant; US = United States of America.

Appendix E Table 22. Results for Depression Symptoms Severity From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ4)

Author, Year	Intervention	Population	Control	FUP, wks	k	N analyzed	Effect	ES (95% CI)	I^2 (%)
Cipriani, 2018[101]	Agomelatine	All participants	Placebo	8	~23	NR	SMD	-0.26 (-0.33 to -0.19)	NR
	Amitriptyline	All participants	Placebo	8	~96	NR	SMD	-0.48 (-0.55 to -0.41)	NR
	Bupropion	All participants	Placebo	8	~33	NR	SMD	-0.25 (-0.33 to -0.16)	NR
	Citalopram	All participants	Placebo	8	~38	NR	SMD	-0.24 (-0.31 to -0.17)	NR
	Clomipramine	All participants	Placebo	8	~20	NR	SMD	-0.33 (-0.45 to -0.21)	NR
Rojas-Garcia, 2015[90]	Combined (Psych+Pharm)	Low SES	UC or EUC	Long-term	3	NR	SMD	-0.47 (-0.97 to 0.03)	85.0
	Combined (Psych+Pharm)	Low SES	UC or EUC	Short-term	3	NR	SMD	-0.68 (-0.97 to -0.40)	55.0
Cipriani, 2018[101]	Desvenlafaxine	All participants	Placebo	8	~9	NR	SMD	-0.25 (-0.35 to -0.15)	NR
	Duloxetine	All participants	Placebo	8	~30	NR	SMD	-0.37 (-0.44 to -0.31)	NR
	Escitalopram	All participants	Placebo	8	~42	NR	SMD	-0.29 (-0.35 to -0.24)	NR
	Fluoxetine	All participants	Placebo	8	~117	NR	SMD	-0.23 (-0.28 to -0.19)	NR
	Fluvoxamine	All participants	Placebo	8	~32	NR	SMD	-0.32 (-0.43 to -0.22)	NR
	Levomilnacipran	All participants	Placebo	8	~6	NR	SMD	-0.27 (-0.40 to -0.13)	NR
	Milnacipran	All participants	Placebo	8	~10	NR	SMD	-0.30 (-0.44 to -0.16)	NR
	Mirtazapine	All participants	Placebo	8	~34	NR	SMD	-0.37 (-0.45 to -0.28)	NR
	Nefazodone	All participants	Placebo	8	~21	NR	SMD	-0.28 (-0.40 to -0.15)	NR
Rojas-Garcia, 2015[90]	Paroxetine	Low SES	Placebo	26	1	63	SMD	-0.39 (-0.74 to -0.04)	NA
	Paroxetine	Low SES	Placebo	13	1	63	SMD	-0.50 (-0.85 to -0.15)	NA
Cipriani, 2018[101]	Paroxetine	All participants	Placebo	8	~114	NR	SMD	-0.32 (-0.37 to -0.28)	NR
	Reboxetine	All participants	Placebo	8	~17	NR	SMD	-0.17 (-0.26 to -0.08)	NR
	Sertraline	All participants	Placebo	8	~54	NR	SMD	-0.27 (-0.34 to -0.21)	NR
Arroll, 2016[99]	SSRI	Primary care-based recruitment	Placebo	NR	NR	NR	SMD	-0.27 (-0.38 to -0.16)	NR
Cipriani, 2018[101]	Trazadone	All participants	Placebo	8	~26	NR	SMD	-0.29 (-0.40 to -0.17)	NR
Arroll, 2016[99]	Tricyclic	Primary care-based recruitment	Placebo	NR	NR	NR	SMD	-0.26 (-0.50 to -0.02)	NR
Cipriani, 2018[101]	Venlafaxine	All participants	Placebo	8	~68	NR	SMD	-0.33 (-0.39 to -0.28)	NR
	Vilazodone	All participants	Placebo	8	~9	NR	SMD	-0.27 (-0.38 to -0.15)	NR
	Vortioxetine	All participants	Placebo	8	~15	NR	SMD	-0.28 (-0.36 to -0.20)	NR

Abbreviations: CI = confidence interval; ES = effect size; EUC = enhanced usual care; FUP = followup; NR = not reported; SES = socioeconomic status; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitor; UC = usual care.

Appendix E Table 23. Results for Depression Remission From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ4)

Author, Year	Intervention	Population	Control	FUP, wks	k	N analyzed	Effect	ES (95% CI)	I^2 (%)
Cipriani, 2018[101]	Agomelatine	All participants	Placebo	8	~23	NR	OR	1.43 (1.24 to 1.65)	NR
	Amitriptyline	All participants	Placebo	8	~96	NR	OR	1.98 (1.73 to 2.25)	NR
	Bupropion	All participants	Placebo	8	~33	NR	OR	1.66 (1.40 to 1.97)	NR
	Citalopram	All participants	Placebo	8	~38	NR	OR	1.37 (1.16 to 1.57)	NR
	Clomipramine	All participants	Placebo	8	~20	NR	OR	1.68 (1.34 to 2.10)	NR
	Desvenlafaxine	All participants	Placebo	8	~9	NR	OR	1.40 (1.16 to 1.70)	NR
	Duloxetine	All participants	Placebo	8	~30	NR	OR	1.78 (1.59 to 1.99)	NR
	Escitalopram	All participants	Placebo	8	~42	NR	OR	1.64 (1.47 to 1.83)	NR
	Fluoxetine	All participants	Placebo	8	~117	NR	OR	1.46 (1.34 to 1.60)	NR
	Fluvoxamine	All participants	Placebo	8	~32	NR	OR	1.66 (1.35 to 2.05)	NR
	Levomilnacipran	All participants	Placebo	8	~6	NR	OR	1.33 (1.03 to 1.73)	NR
	Milnacipran	All participants	Placebo	8	~10	NR	OR	1.53 (1.14 to 2.07)	NR
	Mirtazapine	All participants	Placebo	8	~34	NR	OR	1.66 (1.41 to 1.95)	NR
	Nefazodone	All participants	Placebo	8	~21	NR	OR	1.75 (1.33 to 2.31)	NR
	Paroxetine	All participants	Placebo	8	~114	NR	OR	1.67 (1.53 to 1.82)	NR
	Reboxetine	All participants	Placebo	8	~17	NR	OR	1.23 (1.03 to 1.46)	NR
Viswanathan, 2021[107]	Sertraline	Perinatal	Placebo	8	1	36	RR	2.52 (0.94 to 6.70)	NR

Appendix E Table 23. Results for Depression Remission From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ4)

Author, Year	Intervention	Population	Control	FUP, wks	k	N analyzed	Effect	ES (95% CI)	I^2 (%)
Cipriani, 2018[101]	Sertraline	All participants	Placebo	8	~54	NR	OR	1.52 (1.34 to 1.73)	NR
Arroll, 2016[99]	SSRI	Primary care-based recruitment	Placebo	8	7	1652	RR	1.33 (1.20 to 1.48)	2
Cipriani, 2018[101]	Trazadone	All participants	Placebo	8	~26	NR	OR	1.37 (1.10 to 1.70)	NR
Arroll, 2016[99]	Tricyclic	Primary care-based recruitment	Placebo	8	6	709	RR	1.23 (1.01 to 1.48)	47
Cipriani, 2018[101]	Venlafaxine	All participants	Placebo	8	~68	NR	OR	1.70 (1.54 to 1.89)	NR
	Vilazodone	All participants	Placebo	8	~9	NR	OR	1.47 (1.18 to 1.84)	NR
	Vortioxetine	All participants	Placebo	8	~15	NR	OR	1.49 (1.29 to 1.72)	NR

Abbreviations: CI = confidence interval; ES = effect size; FUP = followup; NR = not reported; OR = odds ratio; SSRI = selective serotonin reuptake inhibitor.

Appendix E Table 24. Results for Response to Depression Treatment From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ4)

Author, Year	Intervention	Population	Control	FUP, wks	k	N analyzed	Effect	ES (95% CI)	I^2 (%)
Cipriani, 2018[101]	Agomelatine	All participants	Placebo	NR	~23	8	OR	1.65 (1.44 to 1.88)	NR
	Amitriptyline	All participants	Placebo	NR	~96	8	OR	2.13 (1.89 to 2.41)	NR
	Bupropion	All participants	Placebo	NR	~33	8	OR	1.58 (1.35 to 1.86)	NR
	Citalopram	All participants	Placebo	NR	~38	8	OR	1.52 (1.33 to 1.74)	NR
	Clomipramine	All participants	Placebo	NR	~20	8	OR	1.49 (1.21 to 1.85)	NR
	Desvenlafaxine	All participants	Placebo	NR	~9	8	OR	1.49 (1.24 to 1.79)	NR
	Duloxetine	All participants	Placebo	NR	~30	8	OR	1.85 (1.66 to 2.07)	NR
	Escitalopram	All participants	Placebo	NR	~42	8	OR	1.68 (1.50 to 1.87)	NR
	Fluoxetine	All participants	Placebo	NR	~117	8	OR	1.52 (1.40 to 1.66)	NR
	Fluvoxamine	All participants	Placebo	NR	~32	8	OR	1.69 (1.41 to 2.02)	NR
	Levomilnacipran	All participants	Placebo	NR	~6	8	OR	1.59 (1.24 to 2.05)	NR
	Milnacipran	All participants	Placebo	NR	~10	8	OR	1.74 (1.37 to 2.23)	NR
	Mirtazapine	All participants	Placebo	NR	~34	8	OR	1.89 (1.64 to 2.20)	NR
	Nefazodone	All participants	Placebo	NR	~21	8	OR	1.67 (1.32 to 2.12)	NR
	Paroxetine	All participants	Placebo	NR	~114	8	OR	1.75 (1.61 to 1.90)	NR
	Reboxetine	All participants	Placebo	NR	~17	8	OR	1.37 (1.16 to 1.63)	NR
	Sertraline	All participants	Placebo	NR	~54	8	OR	1.67 (1.49 to 1.87)	NR
	Trazadone	All participants	Placebo	NR	~26	8	OR	1.51 (1.25 to 1.83)	NR
	Venlafaxine	All participants	Placebo	NR	~68	8	OR	1.78 (1.61 to 1.96)	NR
	Vilazodone	All participants	Placebo	NR	~9	8	OR	1.60 (1.28 to 2.00)	NR
	Vortioxetine	All participants	Placebo	NR	~15	8	OR	1.66 (1.45 to 1.92)	NR

Abbreviations: CI = confidence interval; ES = effect size; FUP = followup; NR = not reported; OR = odds ratio.

Appendix E Table 25. Results for Other Outcomes From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ4)

Author, Year	Intervention	Outcome	Population	Control	FUP, wks	k	N analyzed (IG events, CG events)	Effect	ES (95% CI)	I^2 (%)	KQs	Broad Condition
Krause, 2019[103]	Bupropion	QoL	Older adults	Placebo	10	1	420	SMD	0.17 (-0.03 to 0.36)	NR	KQ4, KQ5	MDD
	Bupropion	Social Fx	Older adults	Placebo	10	1	420	SMD	0.26 (0.06 to 0.45)	NR	KQ4, KQ5	MDD
	Citalopram	QoL	Older adults	Placebo	8	1	175	SMD	-0.06 (-0.37 to 0.25)	NR	KQ4, KQ5	MDD
Baune, 2018[100]	Citalopram	Digit Symbol Substitution Task	All participants	Placebo	Post-tx	1	NR	SMD	-0.04 (-0.33 to 0.26)	NR	KQ4	MDD
Krause, 2019[103]	Duloxetine	QoL	Older adults	Placebo	8	2	NR	SMD	0.14 (-0.04 to 0.33)	NR	KQ4, KQ5	MDD
Baune, 2018[100]	Duloxetine	Digit Symbol Substitution Task	All participants	Placebo	Post-tx	4	NR	SMD	0.13 (-0.03 to 0.28)	NR	KQ4	MDD
	Escitalopram	Digit Symbol Substitution Task	All participants	Placebo	Post-tx	1	NR	SMD	-0.25 (-0.57 to 0.06)	NR	KQ4	MDD
	Nortriptyline	Digit Symbol Substitution Task	All participants	Placebo	Post-tx	1	NR	SMD	0.01 (-0.56 to 0.58)	NR	KQ4	MDD
	Sertraline	Digit Symbol Substitution Task	All participants	Placebo	Post-tx	1	NR	SMD	-0.17 (-0.57 to 0.22)	NR	KQ4	MDD
	Vortioxetine	Digit Symbol Substitution Task	All participants	Placebo	Post-tx	3	NR	SMD	0.34 (0.18 to 0.49)	NR	KQ4	MDD

Abbreviations: CI = confidence interval; ES = effect size; FUP = followup; Fx = functioning; KQ = key question; MDD = major depressive disorder; NR = not reported; QoL = quality of life; SMD = standardized mean difference; tx = treatment.

Appendix E Table 26. Results of Effect Modification Analyses From ESRs of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Outcome Category	Effect mod category	Population	Interv	Control	k	N analyzed	Pooled Risk	Est (95% CI)	I2 (%)	Effect modification results
Naslund, 2018[108]	Other suicide-related	Age	All participants	SSRI	Placebo	NR	NR	NR	NR	NR	Among adults age ≥25 years, the reduction in mean rating of suicidality was larger and the risk for aggravation of suicidality lower in patients receiving SSRI from week 1 and onwards, relatively to placebo, as assessed by item 3 of the HAM-D. In young adults (ages 18-24 years), those given an SSRI were at higher risk for worsening of suicidal ideation (in the unadjusted analysis) or

Appendix E Table 26. Results of Effect Modification Analyses From ESRs of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Outcome Category	Effect mod category	Population	Interv	Control	k	N analyzed	Pooled Risk	Est (95% CI)	I2 (%)	Effect modification results
											emergent suicidality during the late (weeks 3-6) but not the early phase (weeks 1-2) of treatment.
Jakobsen, 2017[109]	Adverse events	Age	All participants	SSRI	Placebo	44	NR	OR	1.39 (1.12 to 1.72)	0.0	Non-elderly: 1.29 (1.01 to 1.65); elderly: 1.75 (1.14 to 2.69)
Rabinowitz, 2016[106]	Depression symptoms	BL depression severity	High BL Depr severity (IPD MA)	AD	Placebo	34	2,760	MD	-2.41 (-3.17 to -1.64)	NR	NR
	Depression symptoms	BL depression severity	Low BL Depr severity (IPD MA)	AD	Placebo	34	4,374	MD	-2.04 (-2.50 to -1.58)	NR	NR
	Depression symptoms	BL depression severity	Medium BL Depr severity (IPD MA)	AD	Placebo	34	3,447	MD	-1.82 (-2.40 to -1.24)	NR	NR
Bighelli, 2018[11]	Depression symptoms	Drug class	All participants (Endpoint)	AD	Placebo	12	1,794	SMD	-0.41 (-0.57 to -0.25)	43	TCA: -0.54, SSRI: -0.27; both stat sig
	Depression symptoms	Drug class	All participants (Mean change)	AD	Placebo	7	1,052	SMD	-0.40 (-0.55 to -0.24)	28	TCA: -0.58, SSRI: -0.36; both stat sig
	Anxiety symptoms	Drug class	All participants	AD	Placebo	12	2,477	SMD	-0.33 (-0.47 to -0.20)	57	Range of SMDs for

Appendix E Table 26. Results of Effect Modification Analyses From ESRs of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Outcome Category	Effect mod category	Population	Interv	Control	k	N analyzed	Pooled Risk	Est (95% CI)	I2 (%)	Effect modification results
			(Mean change)								TCA, SSRI, SNRI: -0.62 to -0.26; SSRI & SNRI stat sig
Bighelli, 2018[11] continued	Anxiety symptoms	Drug class	All participants (Endpoint)	AD	Placebo	17	3,168	SMD	-0.46 (-0.63 to -0.29)	71	TCA: -0.35, SSRI: -0.42 (both p<.05)
	Anxiety symptoms	Drug class	All participants (Mean change)	AD	Placebo	10	2,010	SMD	-0.53 (-0.72 to -0.33)	73	Range of SMDs for TCA, SSRI, SNRI: -2.09 to -0.41; all stat sig
	Anxiety symptoms	Drug class	All participants (Endpoint)	AD	Placebo	15	3,699	SMD	-0.44 (-0.58 to -0.30)	68	Range of SMDs for TCA, SSRI, SNRI: -0.50 to -0.28; all stat sig
	Anxiety symptoms	Drug class	All participants (Endpoint)	AD	Placebo	16	1,671	SMD	-0.43 (-0.66 to -0.20)	78	TCA: -0.83, SSRI: -0.17 (both p<.05)
	Anxiety symptoms	Drug class	All participants (Mean change)	AD	Placebo	8	2,579	SMD	-0.43 (-0.72 to -0.14)	91	Range of SMDs for TCA, SSRI, SNRI: -0.87 to -0.08; SSRI & SNRI stat sig
Bighelli, 2018[11] continued	Anxiety symptoms	Drug class	All participants (Mean change)	AD	Placebo	7	1,792	SMD	-0.68 (-1.19 to -0.17)	96	Range of SMDs for TCA, SSRI, SNRI: -1.22

Appendix E Table 26. Results of Effect Modification Analyses From ESRs of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Outcome Category	Effect mod category	Population	Interv	Control	k	N analyzed	Pooled Risk	Est (95% CI)	I2 (%)	Effect modification results
											to -0.33; TCA & SNRI stat sig
	Anxiety symptoms	Drug class	All participants (Endpoint)	AD	Placebo	13	2,987	SMD	-0.69 (-0.99 to -0.39)	91	TCA: -0.59 (NS), SSRI: -0.50 (p<.05)
	Anxiety response	Drug class	All participants	AD	Placebo	31	6,500	RR	0.72 (0.66 to 0.79)	67	Range of effects for TCA, SSRI, SNRI: 0.61 to 0.75; all stat sig
	Anxiety remission	Drug class	All participants	AD	Placebo	24	6,164	RR	0.83 (0.78 to 0.88)	40	Range of effects for TCA, SSRI, SNRI: 0.82 to 0.84; all stat sig
Hengartner, 2021[110]	Adverse events	Drug class	All participants (Observa-tional studies)	2nd gen	No AD	21	NR	RR	1.87 (1.55 to 2.25)	89.3	SSRI, SNA, Any Unsp: Q=9.39
	Adverse events	Drug class	All participants (Observa-tional studies)	SNA	No AD	21	NR	RR	1.28 (0.90 to 1.80)	96.2	SSRI, SNA, Any Unsp: Q=9.39
Bighelli, 2018[11]	Quality of life	Drug class	All participants	AD	Placebo	6	1,675	SMD	-0.13 (-0.29 to 0.03)	59	SSRI: -0.28 (p
	Functioning	Drug class	All participants (Endpoint)	AD	Placebo	9	1,872	SMD	-0.29 (-0.40 to -0.18)	11	Range of SMDs for TCA, SSRI, SNRI: -0.43

Appendix E Table 26. Results of Effect Modification Analyses From ESRs of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Outcome Category	Effect mod category	Population	Interv	Control	k	N analyzed	Pooled Risk	Est (95% CI)	I2 (%)	Effect modification results
											to -0.15; TCA & SSRI stat sig
	Functioning	Drug class	All participants (Mean change)	AD	Placebo	7	1429	SMD	-0.29 (-0.42 to -0.16)	27	Range of SMDs for TCA, SSRI, SNRI: -0.40 to -0.10; TCA & SSRI stat sig
	Adverse events	Drug class	All participants	AD	Placebo	16	4246	RR	1.11 (1.07 to 1.15)	0.0	Range of effects for TCA, SSRI, SNRI: 1.09 to 1.22; all stat sig
Bighelli, 2018[11] continued	Adverse events	Drug class	All participants	AD	Placebo	33	7,688	RR	1.49 (1.25 to 1.78)	0.0	Range of effects for TCA, SSRI, SNRI: 1.45 to 1.97; all stat sig
	Adverse events	Drug class	All participants	AD	Placebo	40	7,850	RR	0.88 (0.81 to 0.97)	30	Range of effects for TCA, SSRI, SNRI: 0.74 to 0.99; only TCA stat sig
Jacobsen, 2019[111]	Adverse events	Gender	All participants	Citalo-pram	Placebo	1	NR	OR	1.32 (0.89 to 1.94)	NA	Men: 1.48 (0.80 to 2.73); Women: 1.18 (0.71 to 1.96)
	Adverse events	Gender	All participants	Desve-nlafax-	Placebo	3	NR	OR	1.02 (0.84 to 1.25)	NR	Sexual dysfunction

Appendix E Table 26. Results of Effect Modification Analyses From ESRs of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Outcome Category	Effect mod category	Population	Interv	Control	k	N analyzed	Pooled Risk	Est (95% CI)	I2 (%)	Effect modification results
				ine							greater in women. Men: 1.16 (0.50 to 2.69); Women: 1.98 (1.10 to 3.54)
Williams, 2017[13]	Anxiety response	Inclusion of MDD	All participants (Trials include MDD)	SSRI	Placebo	20	2,654	RR	1.77 (1.44 to 2.18)	70	No difference in ES between studies that did and did not include people with MDD
	Anxiety response	Industry funding	All participants (Excl Industry funded)	SSRI	Placebo	16	1,780	RR	1.99 (1.43 to 2.77)	77	No difference in ES between industry funded and non-industry funded
Cuijpers, 2015[102]	Depression symptoms	Publication bias	All participants	Psych + Pharm	Pill placebo	6	NR	Hedges' g	-0.46 (-0.70 to -0.21)	17	Estimated effect adjusted for possible publication bias via Duvall and Tweedie's procedure: g=-0.31, 95% CI -0.60 to -0.01
Lisinski,	Depression	See	All	Dulox	Placebo	NR	NR	NR	NR	NR	Greater

Appendix E Table 26. Results of Effect Modification Analyses From ESRs of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Outcome Category	Effect mod category	Population	Interv	Control	k	N analyzed	Pooled Risk	Est (95% CI)	I2 (%)	Effect modification results
2020[105]	symptoms	narrative	participants	etine							difference between duloxetine and placebo for suicidality items among adults age 25 and older vs. those age 18-24; between-group differences were only statistically significant in adults age 25 and older. Greater symptom reduction with duloxetine
Krause, 2019[103]	Depression symptoms	See narrative	Older adults	Dulox-etine	Placebo	1	NR	SMD	-0.39 (-0.64 to -0.14)	NR	Subgroup and meta-regression analyses showed no statistically significant impact on the response rates for the moderators mean age, study

Appendix E Table 26. Results of Effect Modification Analyses From ESRs of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Outcome Category	Effect mod category	Population	Interv	Control	k	N analyzed	Pooled Risk	Est (95% CI)	I2 (%)	Effect modification results
											duration, sponsorship or publication year. Neither had the sensitivity analyses excluding studies with high risk in the various risk of bias domains.
Krause, 2019[103]	Depression remission	See narrative	Older adults	Dulox-etine	Placebo	1	NR	RR	1.57 (0.95 to 2.59)	NR	Subgroup and meta-regression analyses showed no statistically significant impact on the response rates for the moderators mean age, study duration, sponsorship or publication year. Neither had the sensitivity analyses excluding

Appendix E Table 26. Results of Effect Modification Analyses From ESRs of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Outcome Category	Effect mod category	Population	Interv	Control	k	N analyzed	Pooled Risk	Est (95% CI)	I2 (%)	Effect modification results
											studies with high risk in the various risk of bias domains.
Cipriani, 2018[101]	Depression response	See narrative	All participants	AD	Placebo	NR	NR	NR	NR	NR	Smaller studies and older studies presented larger effects of the active interventionsvs. placebo, in particular for amitriptyline, buproprion, fluoxetine, and reboxetine. Studies with patients with more severe depression showed larger effectiveness than studies with low/moderate depression, with fluvoxamine showing this relationship most strongly, although there

Appendix E Table 26. Results of Effect Modification Analyses From ESRs of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Outcome Category	Effect mod category	Population	Interv	Control	k	N analyzed	Pooled Risk	Est (95% CI)	I2 (%)	Effect modification results
											is a risk of ecological bias for all agents, leading to inconclusive results. No association with industry sponsorship or with publication status (published vs. unpublished) was detected, however there appeared to be limited ability to detect impact of these characteristics.
Jacobsen, 2019[111]	Adverse events	Sex	All participants	Vilazo done	Placebo	3	NR	OR	1.11 (0.91 to 1.35)	NR	Sexual dysfunction greater in men. Men: 1.42 (1.04 to 1.93); Women: 0.92 (0.71 to 1.19)

Abbreviations: AD = antidepressant; BL = baseline; CI = confidence interval; ES = effect size; IPD MA = individual patient data meta-analysis; MD = mean difference; MDD = major depressive disorder; NR = not reported; OR = odds ratio; RR = relative risk; TCA = tricyclic antidepressant; SMD = standardized mean difference; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Appendix E Table 27. Results of Narrative Syntheses From ESRs of Pharmacologic Treatment of Depression (KQ4)

Author, Year	Intervention	Population	Outcome	Findings
Cipriani, 2018[101]	Antidepressants	All participants	Depression response	Smaller studies and older studies presented larger effects of the active interventions vs. placebo, in particular for amitriptyline, bupropion, fluoxetine, and reboxetine. Studies with patients with more severe depression showed larger effectiveness than studies with low/moderate depression, with fluvoxamine showing this relationship most strongly, although there is a risk of ecological bias for all agents, leading to inconclusive results. No association with industry sponsorship or with publication status (published vs. unpublished) was detected, however there appeared to be limited ability to detect impact of these characteristics.
Lee, 2018[104]	Antidepressants	All participants	Occupational fx	Thirteen placebo-controlled and four active comparator clinical trials reported on the efficacy of agomelatine, bupropion, desvenlafaxine, duloxetine, fluoxetine, levomilnacipran, paroxetine, sertraline, venlafaxine, or vortioxetine on subjective measures of workplace impairment. Overall, antidepressant treatment improved standardized measures of workplace functioning (e.g., Sheehan Disability Scale-work item). One placebo-controlled trial of agomelatine reported reduced number of days work lost in past week (p<.001).
Lisinski, 2020[105]	Duloxetine	All participants	Depression symptoms	Greater difference between duloxetine and placebo for suicidality items among adults age 25 and older vs. those ages 18-24; between-group differences were only statistically significant in adults age 25 and older. Greater symptom reduction with duloxetine than placebo was present in patients with and without early side effects, although effect size was larger among those reporting early side effects (p=.02). No association between baseline severity and change in the overall HAM-D or when combining 6 items representing core depression symptoms; however, there was a larger group difference when combining the remaining (non-core) items (p=.02).
	Duloxetine	All participants	Depression symptoms	14 of 17 HAM-D items showed greater improvement with duloxetine vs placebo at week 8.

Abbreviations: ESRs = existing systematic reviews; fx = functioning**;** HAM-D = Hamilton Rating Scale for Depression.

Appendix E Table 28. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ5)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Cuijpers, 2018b[112]	Depression could be established with a diagnostic interview or with a score above a cutoff on a self-report measure	Psychological treatment of depression, defined as having a primary focus on language-based communication between a patient and a therapist, or as bibliotherapy supported by a therapist.	Control group (waiting list, care-as-usual, placebo, other inactive treatment)	Outpatient settings	Clinically significant deterioration: We allowed any definition, as long as it indicated the proportion of patients in therapy and control groups who scored higher on depression symptom severity after treatment than they did at baseline, and as long as the authors described this as an indication for clinically significant deterioration.
Ebert, 2016[113]	Adults (age ≥18 years) with depression (established by diagnostic interview or elevated levels of depressive symptoms on self-report measures).	Internet-based guided self-help treatment	Control or comparison group (waiting list, care-as-usual, other)	NR	Deterioration rate: All studies used either the Centre for Epidemiological Studies – Depression Scale (CES-D) or the Beck Depression Inventory (BDI) as outcome measures. Where multiple depression measures were present, the BDI was coded as the primary outcome measure given that it was the most frequently used outcome measure across studies. For both measures we calculated deterioration and response rates according to the widely used reliable change index (RCI). Participants whose scores from pre-treatment to post-treatment had RCIs below the cut point of -1.96 were considered to have experienced deterioration.

Appendix E Table 28. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Depression (KQ5)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Jonsson, 2016[98]	Age 65 years or older and either be formally diagnosed with a depressive disorder in accordance with the definitions by American Psychiatric Association and the World Health Organization, or have significant depressive symptoms as measured with a validated scale.	Any psychological treatment, defined as an intervention based on an explicit psychological theory.	Any comparator (e.g., any alternative treatment, waitlist, or placebo)	Any setting	Any adverse events (any validated measure of was acceptable)
Karyotaki, 2018b[114]	Adults (age ≥18 years) with symptoms of depression based either on a diagnostic interview or validated self-report scales.	Self-guided iCBT	Control condition (waiting list, treatment as usual, attention placebo or other non-active controls)	NR	Deterioration rate: The included studies used either the Beck Depression Inventory (BDI or BDI-II), the Centre for Epidemiological Studies Depression Scale (CES-D), or the Patient Health Questionnaire (PHQ-9) as outcome measures of depression severity. We classified "clinically significant deterioration" according to each participant's reliable change index (RCI). Participants showing a clinically significant change with an increase in their score (clinically significant negative change of more than -1.96) were classified as clinically significantly deteriorated.

Abbreviations: iCBT = internet cognitive behavioral therapy; NR = not reported.

Appendix E Table 29. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Harms of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Braun, 2016[115]	Studies on patients with depressive disorders (diagnosed with a commonly applied diagnostic system)	Studies on patients randomized to receive antidepressants for at least 3 months' duration	Placebo	NR	Although in these studies the main outcomes were psychopathological variables, we restricted our selection process to studies reporting on suicides (primary outcome) and suicide attempts (secondary outcome) during treatment.
Chan, 2019[116]	Users of antidepressants	Antidepressants	NR	NR	Diagnosis of MCI or dementia using validated diagnostic criteria (e.g., ICD-10 or DSM-IV-TR)
Cipriani, 2018[101]	Adults (age ≥18 years) with a primary diagnosis of MDD according to standard diagnostic criteria (Feighner criteria, Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV, DSM-5, and ICD-10)	RCTs comparing antidepressants with placebo or another active antidepressant as oral monotherapy for the acute treatment of adults with primary diagnosis of MDD. Additionally, included all second-generation antidepressants approved by the regulatory agencies in the US, Europe, or Japan: agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine,	Placebo or another active antidepressant as oral monotherapy	NR	Efficacy (response rate measured by the total number of patients who had a reduction of ≥50% of the total score on a standardized observer-rating scale for depression) and acceptability (treatment discontinuation measured by the proportion of patients who withdrew for any reason). When depressive symptoms had been measured with more than one standardized rating

Appendix E Table 29. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Harms of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
		escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine, vilazodone, and vortioxetine; two tricyclics (amitriptyline and clomipramine); trazodone and nefazodone. Additionally, included trials that allowed rescue medications so long as they were equally provided among the randomized groups			scale, we used a predefined hierarchy, based on psychometric properties and consistency of use. 8-week outcomes were selected if available, or the closest to 8 weeks (within 4-12 weeks).
Gibbons, 2012[117]	NR	Fluoxetine or venlafaxine	Placebo	NR	HAM-D item 3 (score of 2 or greater), and item 13 of the CDRS-R (score of 2 or greater); AERs of suicide attempts and suicide from studies
Gumusoglu, 2022[118]	Observational studies of preeclampsia risk or gestational hypertension given SSRI use in pregnancy.	Exposure group was women who were exposed to SSRIs (all types) during pregnancy	Those who were unexposed to SSRIs.	No language or location restrictions	Gestational hypertension or preeclampsia

Appendix E Table 29. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Harms of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Hengartner, 2021[110]	Adults (age ≥18 years) with depression and any unspecified condition reporting suicide risk for patients exposed to SSRI or new-generation serotonergic-noradrenergic ADs relative to unexposed patients. Also included studies reporting risk estimates for any unspecified antidepressant class when it was possible to infer from the data or external sources (e.g., prescription rates for different antidepressant classes in the underlying population) that at least 75% of all prescriptions in the study sample were SSRI or SNA.	Studies with patients exposed to SSRI or new-generation serotonergic-noradrenergic ADs relative to unexposed patients. Required exposed and unexposed groups to be broadly comparable in terms of clinical and socioeconomic characteristics	NR	NR	Primary outcomes were the risk of suicide and suicide attempt in people exposed to new-generation antidepressants relative to an unexposed group according to the statistically best-adjusted analysis reported in the primary study
Jacobsen, 2019[111]	Patients at least age 18 years being treated for depression	Antidepressant approved by FDA for treatment of depression used within approved dosage range	placebo	NR	Validated sexual functioning questionnaire
Jakobsen, 2017[109]	Participants had to be 18 years or older and have a primary diagnosis of major depressive disorder based on standardized criteria such as DSM III, DSM III-R, DSM IV, DSM V, or ICD 10	SSRI	Placebo, active placebo, or no intervention	NR	Serious adverse events (medical events that were life threatening, resulted in death, disability, significant loss of function, or caused hospital admission or prolonged hospitalization); suicides, suicide attempts, and suicide ideation

Appendix E Table 29. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Harms of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Jensen, 2019[119]	NR	SSRI	Placebo or non-treatment	NR	Intracranial hemorrhage, hemorrhagic stroke, or intracerebral hemorrhage
Kaminski, 2020[120]	Used the US FDA database (http://www.accessdata.fda.gov/) (FDA ACCESS DATA 2016): The Integrated Safety Summary data from approval packets for 14 investigational antidepressant programs (1991–2013, 40,857 patients, 10,890.5 exposure years) were used to calculate suicides and suicide attempts per 100,000 patient exposure years (standardized rates) for antidepressant and placebo treatment groups separately. For this analysis, we included programs for investigational antidepressants or new molecular formulations (such as extended-release formulations) of antidepressants indicated for the treatment of major depressive disorder (MDD) in adults (age >18 years).	Antidepressant	Placebo	NR	Death by suicide: the raw number of completed and confirmed deaths by suicide was reported for each program and treatment assignment. These deaths were judged by a medical examiner to be caused by suicide. Suicide attempts: we were able to record the number of suicide attempts for those ISS reports that tabulated suicidal attempts as a separate category of adverse events.
Khanassov, 2018[121]	Adults on an SSRI or SNRI, with or without a formal diagnosis of depression	SSRI or SNRI use (e.g., fluoxetine, citalopram, escitalopram, paroxetine, sertraline, fluvoxamine, venlafaxine, duloxetine (a full list is provided in Supplementary	None or some other form of anti-depressant treatment	NR	Fracture (any type of fracture at any anatomical sites either self-reported or identified in the hospital records)

Appendix E Table 29. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Harms of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
		material).			
KoKoAung, 2015[122]	Studies that included older people age 60 years and older, regardless of gender or ethnic background, with DSM-IV or equivalent diagnostic criteria for Major Depressive Disorder (MDD) without psychotic features. The review considered both community and hospitalized older patients with stable medical co-morbidities.	Any SSRI medication including oral fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine with a clinically effective dose recommended by the manufacturer for older people for a minimum duration of four weeks.	Comparators included placebo or a different class of ADs including monoamine oxidase inhibitors or tricyclic antidepressants	NR	Primary outcomes: worsening or emergent suicidal ideation, attempted suicide, and completed suicide. Study reports on suicide attempt, completed suicide, and changes on the suicide item in depression rating scales were used to measure primary outcome data. The term “suicide attempt” referred to potentially self-injurious behavior with a non-fatal outcome.
Krause, 2019[103]	Age 65 years and older	Any pharmacologic or non-pharmacologic intervention (included only for pharmacologic evidence; non-pharmacologic superseded by other reviews)	NR	Excluded studies from mainland China; studies before 1990	At least 50% reduction on the HAM-D, MADRS, BDI, or any other validated depression scale; or "much or very much improved" (score 1 or 2) on CGI improvement; number of participants in remission; depressive symptoms at endpoint/mean reduction of depressive symptoms from baseline to endpoint; dropouts owing to any reason (all-cause

Appendix E Table 29. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Harms of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
					discontinuation), dropouts owing to inefficacy of treatment and dropouts due to adverse events. Further efficacy outcomes we analyzed were quality of life and social functioning
Kunutsor, 2018[123]	Adults with depression or antidepressant use with first VTE, DVT (deep vein thrombosis), or PE (pulmonary embolism) events	Antidepressant use	NR	NR	Primary outcome was composite of VTE (DVT and/or PE), as reported by each study. Number of cases of VTE, DVT, and/or PE were extracted. Risk estimates for the greatest degree of adjustment were extracted.
Maslej, 2017[124]	Users of prescribed antidepressants	Any class or combination of antidepressant used in any dose or duration	Group not taking antidepressants	NR	All-cause mortality excluding overdose cases
Na, 2018[125]	NR	Bupropion or mirtazapine use	NR	NR	Bleeding events
Naslund, 2018[108]	Adults (age >18 years) included in SSRI trials	SSRI (regardless of drug and dose)	Placebo	Industry-sponsored, HRSD-based, FDA-registered placebo-controlled studies,	HRSD item 3: 1) higher rating than baseline (worsening), 2) rating of 2-4 during treatment in participant with baseline rating of 0 or 1 ("emergency suicidality: loose definition"), and 3)

Appendix E Table 29. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Harms of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
				post-registration, or post marketing trials	rating of 3-4 during treatment in participant with a rating of 0 or 1 at baseline ("emergency suicidality: strict definition")
Sobieraj, 2019[126]	Patients age 65 years and older with MDD	Studies that compared one antidepressant with another antidepressant, placebo, or nonpharmacologic therapy. We included the following antidepressants as interventions: SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), SNRIs (desvenlafaxine, duloxetine, levomilnacipran, milnacipran, and venlafaxine), and other antidepressants including bupropion, mirtazapine, trazodone, vilazodone, and vortioxetine.	Other antidepressants, placebo, or nonpharmacologic therapy. TCAs or monoamine oxidase inhibitors were allowed.	Studies were required to be conducted in a nonacute care setting such as a specialist or generalist outpatient setting, rehabilitation facility, or nursing facility.	Any serious event during the study: bleeding, blood pressure (changes in blood pressure, orthostatic blood pressure), cognitive measures (cognitive impairment, cognitive function), electrocardiogram-related outcomes (arrhythmias, QTc prolongation), emergency department visits, falls, fractures, hospitalizations, mortality, seizures, serious adverse events (as defined per the study), suicide/suicide attempt, suicidal thoughts, SIADH or hyponatremia, weight changes, or number of subjects who withdrew from the study due to an adverse event

Appendix E Table 29. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Harms of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Trajkova, 2019[127]	Adults	Any use of antidepressant medication	NR	NR	Incident fatal/nonfatal stroke and recurrent strokes
Viswanathan, 2021[107]	For tx: Studies in women who are pregnant or postpartum with new or preexisting diagnosis of anxiety, depression, bipolar disorder, or schizophrenia; For tx harms: Reproductive-aged women (ages 15-44 years during preconception [≤12 weeks before pregnancy], pregnancy, and postpartum [through 1 year]) with any mental health disorder (new or preexisting)	All US FDA-approved drugs for mental health disorders and off-label drugs used for mental health disorders were eligible	Placebo or no tx, or other pharmacologic interventions	NR	Outcomes included maternal benefits (symptoms, functional capacity, quality of life, delivery mode, breastfeeding, weight change, change in suicidal events); maternal harms (miscarriage, abruption, preterm labor/preterm birth, preeclampsia, gestational hypertensive disorders, gestational diabetes mellitus); and fetal, infant, or child harms (preterm birth, small or large for gestational age, congenital anomalies, Apgar score, withdrawal, respiratory distress, neonatal intensive care unit time, persistent pulmonary hypertension, delayed development, child mental health disorders, and death).

Appendix E Table 29. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Harms of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Vlenterie, 2021[128]	Studies included if they examined associations of depression, depressive symptoms, or use of antidepressants during pregnancy with gestational age, birth weight, SGA, or Apgar scores. Study population was divided into four partly overlapping cohorts: 1) depression cohort—all women with information on the presence of depressive symptoms or a clinical diagnosis of depression; 2) restricted depression cohort—depression cohort, excluding women who used antidepressants during pregnancy and those for whom no information was available about antidepressant use; 3) antidepressant use cohort—all women with information on AD use; and 4) restricted AD use cohort—antidepressant use cohort, excluding women without depressive symptoms or a clinical diagnosis of depression.	NR	NR	NR	Requested continuous exposure data on depressive symptoms collected via self-completed questionnaires, including the Center for Epidemiological Studies Depression Scale, the Edinburgh Postpartum Depression Scale (that is also called the Edinburgh Depression Scale, General Health Questionnaire, Patient Health Questionnaire-9, Primary Care Evaluation of Mental Disorders Patient Questionnaire, Brief Symptom Inventory, and Hopkins Symptoms Check list. Standardized instrument-specific cut-off values were used to dichotomize these data for presence or absence of depressive symptoms. Data on clinical diagnoses of depression and antidepressant use were delivered dichotomously. The exposure time windows were divided into trimesters of pregnancy, and the

Appendix E Table 29. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Harms of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
					types of ADs were divided into selective serotonin reuptake inhibitors (SSRIs), tricyclic ADs, and mirtazapine.
Wang, 2018[129]	Mean age >50 years	Use of antidepressants, selective serotonin reuptake inhibitor (SSRI); tricyclic (TCA); and monoamine oxidase inhibitor (MAOI)	Nonusers of antidepressants	NR	Combined abstracted ORs and HRs to impute a common estimate of RR for development of dementia associated with use of SSRI

Abbreviations: AD(s) = antidepressant(s); BDI = Beck Depression Inventory; CGI = Clinical Global Impressions scale; DSM = Diagnostic and Statistical Manual; FDA = Food and Drug Administration; HAM-D = Hamilton Depression Rating scale; HR = hazard ratio; ICD = International Classification of Disease; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; NEWMEDS = Novel methods leading to new medications in depression and schizophrenia; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RR = risk ratio; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA or TeCA = tricyclic antidepressant; US = United States of America,

Appendix E Table 30. Results of Narrative Syntheses From ESRs of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Intervention	Population	Outcome	Findings
Viswanathan, 2021[107]	Pharmacologic	Perinatal	Serious AEs	Although many studies report on adverse events, they could not rule out underlying disease severity as the cause of the association between exposures and adverse events. Five RCTs and 70 observational studies were included, reporting on 27 potential serious adverse events (including maternal, birth, and infant/child harms). The authors judged the certainty of evidence to draw conclusions to be insufficient or low in all instances (Table 3 in journal publication), including congenital and cardiac anomalies (graded insufficient), primarily because of lack of control for confounding. Table 2 (in journal publication) indicates no more than small absolute risk differences for all adverse events.
Gibbons, 2012[117]	Antidepressants	All participants	Suicidal ideation	Fluoxetine and venlafaxine decreased suicidal thoughts and behavior for adult and geriatric patients. This protective effect is mediated by decreases in depressive symptoms with treatment.
KoKoAung, 2015[122]	SSRI	Older adults	Suicide deaths	One cohort study limited to people with depression showed a benefit (RR=0.64 [95% CI, 0.38 to 1.07]), but one cohort study not limited to people with depression showed a harm (RR=4.87 [95% CI, 1.99 to 11.94]).
	SSRI	Older adults	Suicide attempts	3 studies with effect ranging from benefit among depressed patients, SSRI vs. no AD (RR, 0.38 [95% CI, 0.16 to 0.91]) to harm when not limited to depressed patients, SSRI vs. no SSRI (RR, 2.16 [95% CI, 1.72 to 2.72). Largest study showed harm among depression patients, SSRI prescription vs. no SSRI prescription (RR, 1.12 [95% CI, 1.04 to 1.21]).
Naslund, 2018[108]	SSRI	All participants	Suicidality	Among adults age 25 and older, the reduction in mean rating of suicidality was larger and the risk for aggravation of suicidality lower in patients receiving SSRI from week 1 and onwards, relative to placebo, as assessed by item 3 of the HAM-D. In young adults (ages 18-24 years), those given an SSRI were at higher risk for worsening of suicidal ideation (in the unadjusted analysis) or emergent suicidality during the late (weeks 3-6) but not the early phase (weeks 1-2) of treatment.

Appendix E Table 30. Results of Narrative Syntheses From ESRs of Pharmacologic Treatment of Depression (KQ5)

Author, Year	Intervention	Population	Outcome	Findings
Jakobsen, 2017[109]	SSRI	All participants	Any adverse events	Most common adverse effects (all p<.05 for group differences): abnormal ejaculation, tremor, anorexia, nausea, somnolence, sweating, asthenia, diarrhea, constipation, insomnia, dizziness, dry mouth, libido decreased, sexual dysfunction, appetite decreased, fatigue, vomiting or upset stomach, flu syndrome, drowsiness, blurred/abnormal vision or dry eyes, nervousness, back pain, headache, dyspepsia, weight loss. Up to 78 studies per outcome.
Khanassov, 2018[121]	SNRI	All participants	Fractures	2 of 6 studies reported statistically significantly higher risk of fracture with SNRI use (details not available). No meta-analysis conducted due to excessive heterogeneity and limited number of studies.

Abbreviations: AD = antidepressant; AE = adverse event; CI =confidence interval; ESR = existing systematic review; HAM-D = Hamilton Rating Scale for Depression; RCT = randomized controlled trial; RR = risk ratio; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Appendix E Table 31. Results for Any Adverse Events From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	FUP, wks	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Sobieraj, 2019[126]	SSRI	Any adverse events	Older	Placebo	12-48	1	53/130 (40.8)	54/91 (59.3)	RR	0.69 (0.53 to 0.90)	NA
	SSRI	Any adverse events	Older	Placebo	12+	2	275/437 (62.9)	179/276 (64.9)	RR	1.07 (0.98 to 1.16)	0
Jakobsen, 2017[109]	SSRI	Any adverse events	All	Placebo	Post-tx	NR	NR	NR	NR	NR	NR
Sobieraj, 2019[126]	SSRI	Any adverse events (Cohort study)	Older	No AD	NR	1	NR/NR (NR)	NR/NR (NR)	HR	1.20 (1.02 to 1.42)	NR
	SNRI	Any adverse events	Older	Placebo	12+	3	359/460 (78.0)	239/345 (69.3)	RR	1.14 (1.03 to 1.25)	36
	Venlafaxine	Any adverse events (Cohort study)	Older	No AD	NR	1	NR/NR (NR)	NR/NR (NR)	HR	0.89 (0.55 to 1.46)	NR
	Vortioxetine	Any adverse events	Older	Placebo	12+	1	97/156 (62.2)	89/145 (61.4)	RR	1.01 (0.85 to 1.21)	NR
	Bupropion	Any adverse events	Older	Placebo	12+	1	121/211 (57.3)	122/207 (58.9)	RR	0.97 (0.83 to 1.14)	NR
	Mirtazapine	Any adverse events (Cohort study)	Older	No AD	NR	1	NR/NR (NR)	NR/NR (NR)	HR	1.02 (0.64 to 1.69)	NR
	Trazadone	Any adverse events (Cohort study)	Older	No AD	NR	1	NR/NR (NR)	NR/NR (NR)	HR	1.06 (0.50 to 2.24)	NR

*Evidence is based on RCTs unless specified otherwise.

Abbreviations: AD = antidepressant; CG = control group; CI = confidence interval; ES = effect size; FUP = followup; HR = hazard ratio; IG = intervention group; NA = not applicable; NR = not reported; RR = risk ratio; SSRI = selective serotonin reuptake inhibitor; tx = treatment.

Appendix E Table 32. Results for Dropout for Any Reason From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	Followup	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Cipriani, 2018[101]	Citalopram	Dropout for any reason	All	Placebo	8	~38	NR	NR	OR	0.94 (0.80 to 1.09)	NR
	Escitalopram	Dropout for any reason	All	Placebo	8	~42	NR	NR	OR	0.90 (0.80 to 1.02)	NR
	Fluoxetine	Dropout for any reason	All	Placebo	8	~117	NR	NR	OR	0.88 (0.80 to 0.96)	NR
Krause, 2019[103]	Fluoxetine	Dropout for any reason	Older	Placebo	8	2	NR	NR	RR	1.49 (1.05 to 2.13)	NR
Cipriani, 2018[101]	Fluvoxamine	Dropout for any reason	All	Placebo	8	~32	NR	NR	OR	1.10 (0.91 to 1.33)	NR
	Paroxetine	Dropout for any reason	All	Placebo	8	~114	NR	NR	OR	0.95 (0.87 to 1.03)	NR
	Sertraline	Dropout for any reason	All	Placebo	8	~54	NR	NR	OR	0.96 (0.85 to 1.08)	NR
	Desvenlafaxine	Dropout for any reason	All	Placebo	8	~9	NR	NR	OR	1.08 (0.88 to 1.33)	NR
	Duloxetine	Dropout for any reason	All	Placebo	8	~30	NR	NR	OR	1.09 (0.96 to 1.23)	NR
	Levomilnacipran	Dropout for any reason	All	Placebo	8	~6	NR	NR	OR	1.19 (0.93 to 1.53)	NR
	Milnacipran	Dropout for any reason	All	Placebo	8	~10	NR	NR	OR	0.95 (0.73 to 1.26)	NR
	Venlafaxine	Dropout for any reason	All	Placebo	8	~68	NR	NR	OR	1.04 (0.93 to 1.15)	NR
	Reboxetine	Dropout for any reason	All	Placebo	8	~17	NR	NR	OR	1.16 (0.96 to 1.40)	NR
	Vortioxetine	Dropout for any reason	All	Placebo	8	~15	NR	NR	OR	1.01 (0.86 to 1.19)	NR
	Vilazodone	Dropout for any reason	All	Placebo	8	~9	NR	NR	OR	1.14 (0.88 to 1.47)	NR
	Nefazodone	Dropout for any reason	All	Placebo	8	~21	NR	NR	OR	0.93 (0.72 to 1.19)	NR
	Bupropion	Dropout for any reason	All	Placebo	8	~33	NR	NR	OR	0.96 (0.81 to 1.14)	NR

Appendix E Table 32. Results for Dropout for Any Reason From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	Followup	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
	Mirtazapine	Dropout for any reason	All	Placebo	8	~34	NR	NR	OR	0.99 (0.85 to 1.15)	NR
	Amitriptyline	Dropout for any reason	All	Placebo	8	~96	NR	NR	OR	0.95 (0.83 to 1.08)	NR
Krause, 2019[103]	Amitriptyline	Dropout for any reason	Older	Placebo	NR	NR	NR	NR	RR	1.81 (1.05 to 3.12)	NR
Cipriani, 2018[101]	Clomipramine	Dropout for any reason	All	Placebo	8	~20	NR	NR	OR	1.30 (1.01 to 1.68)	NR
	Trazadone	Dropout for any reason	All	Placebo	8	~26	NR	NR	OR	1.15 (0.93 to 1.42)	NR
	Agomelatine	Dropout for any reason	All	Placebo	8	~23	/ ()	/ ()	OR	0.84 (0.72 to 0.97)	NR

*Evidence is based on RCTs unless specified otherwise.

Abbreviations: CG = control group; CI = confidence interval; ES = effect size; IG = intervention group; NR = not reported; OR = odds ratio; RCT = randomized controlled trial.

Appendix E Table 33. Results for Dropout Due to Adverse Events From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	Followup	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Sobieraj, 2019[126]	SSRI	Dropout due to AE	Older	Placebo	12+	3	65/521 (12.5)	15/366 (4.1)	RR	2.90 (1.16 to 5.06)	0
Cipriani, 2018[101]	Citalopram	Dropout due to AE	All	Placebo	8	~38	NR	NR	OR	1.87 (1.39 to 2.51)	NR
Sobieraj, 2019[126]	Escitalopram	Dropout due to AE	Older	Placebo	48+	2	7/95 (7.4)	8/79 (10.1)	RR	.81 (.31 to 2.11)	0
Cipriani, 2018[101]	Escitalopram	Dropout due to AE	All	Placebo	8	~42	NR	NR	OR	1.72 (1.38 to 2.14)	NR
Sobieraj, 2019[126]	Escitalopram	Dropout due to AE	Older	Placebo	12-48	1	4/152 (2.6)	7/153 (4.6)	RR	.58 (.17 to 1.92)	NA
Krause, 2019[103]	Escitalopram	Dropout due to AE	Older	Placebo	8	3	NR	NR	RR	2.07 (1.09 to 3.94)	NR
Cipriani, 2018[101]	Fluoxetine	Dropout due to AE	All	Placebo	8	~117	NR	NR	OR	1.82 (1.56 to 2.13)	NR
Krause, 2019[103]	Fluoxetine	Dropout due to AE	Older	Placebo	8	2	NR	NR	RR	2.53 (1.49 to 4.29)	NR
Cipriani, 2018[101]	Fluvoxamine	Dropout due to AE	All	Placebo	8	~32	NR	NR	OR	2.83 (2.12 to 3.80)	NR
	Paroxetine	Dropout due to AE	All	Placebo	8	~114	NR	NR	OR	2.19 (1.90 to 2.53)	NR
Krause, 2019[103]	Paroxetine	Dropout due to AE	Older	Placebo	NR	NR	NR	NR	RR	2.62 (1.13 to 6.10)	NR
Cipriani, 2018[101]	Sertraline	Dropout due to AE	All	Placebo	8	~54	NR	NR	OR	2.01 (1.61 to 2.52)	NR
Krause, 2019[103]	Sertraline	Dropout due to AE	Older	Placebo	NR	NR	NR	NR	RR	2.22 (1.03 to 4.80)	NR
Sobieraj, 2019[126]	SNRI	Dropout due to AE	Older	Placebo	12+	3	56/467 (12.0)	22/345 (6.4)	RR	1.85 (1.05 to 3.27)	NR
Cipriani, 2018[101]	Desvenlafaxine	Dropout due to AE	All	Placebo	8	~9	NR	NR	OR	1.66 (1.14 to 2.44)	NR
	Duloxetine	Dropout due to AE	All	Placebo	8	~30	NR	NR	OR	2.48 (2.02 to 3.06)	NR
Sobieraj, 2019[126]	Duloxetine	Dropout due to AE	Older	Placebo	2-48	1	38/249 (15.3)	4/121 (3.3)	RR	2.64 (1.21 to 5.73)	NR

Appendix E Table 33. Results for Dropout Due to Adverse Events From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	Followup	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Krause, 2019[103]	Duloxetine	Dropout due to AE	Older	Placebo	8	2	NR	NR	RR	1.68 (1.03 to 2.75)	NR
Cipriani, 2018[101]	Levomilnacipran	Dropout due to AE	All	Placebo	8	~6	NR	NR	OR	2.57 (1.64 to 4.13)	NR
	Milnacipran	Dropout due to AE	All	Placebo	8	~10	NR	NR	OR	1.64 (1.06 to 2.52)	NR
	Venlafaxine	Dropout due to AE	All	Placebo	8	~68	NR	NR	OR	2.95 (2.49 to 3.51)	NR
Krause, 2019[103]	Venlafaxine	Dropout due to AE	Older	Placebo	8	1	NR	NR	RR	3.07 (1.67 to 5.62)	NR
Cipriani, 2018[101]	Reboxetine	Dropout due to AE	All	Placebo	8	~17	NR	NR	OR	2.73 (2.02 to 3.69)	NR
Sobieraj, 2019[126]	Vortioxetine	Dropout due to AE	Older	Placebo	12+	1	9/156 (5.8)	4/145 (2.8)	RR	2.09 (.66 to 6.64)	NR
Cipriani, 2018[101]	Vortioxetine	Dropout due to AE	All	Placebo	8	~15	NR	NR	OR	1.64 (1.25 to 2.14)	NR
	Vilazodone	Dropout due to AE	All	Placebo	8	~9	NR	NR	OR	2.26 (1.40 to 3.66)	NR
	Nefazodone	Dropout due to AE	All	Placebo	8	~21	NR	NR	OR	2.18 (1.49 to 3.18)	NR
	Bupropion	Dropout due to AE	All	Placebo	8	~33	NR	NR	OR	2.28 (1.68 to 3.10)	NR
Sobieraj, 2019[126]	Bupropion	Dropout due to AE	Older	Placebo	12+	1	17/211 (8.1)	22/207 (10.6)	RR	.76 (.41 to 1.39)	NR
Cipriani, 2018[101]	Mirtazapine	Dropout due to AE	All	Placebo	8	~34	NR	NR	OR	2.21 (1.74 to 2.81)	NR
	Amitriptyline	Dropout due to AE	All	Placebo	8	~96	NR	NR	OR	3.11 (2.54 to 3.82)	NR
Krause, 2019[103]	Amitriptyline	Dropout due to AE	Older	Placebo	NR	NR	NR	NR	RR	2.81 (1.28 to 6.18)	NR
Cipriani, 2018[101]	Clomipramine	Dropout due to AE	All	Placebo	8	~20	NR	NR	OR	4.44 (3.07 to 6.50)	NR
Krause, 2019[103]	Nortriptyline	Dropout due to AE	Older	Placebo	NR	NR	NR	NR	RR	3.68 (1.15 to 11.76)	NR

Appendix E Table 33. Results for Dropout Due to Adverse Events From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	Followup	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Cipriani, 2018[101]	Trazadone	Dropout due to AE	All	Placebo	8	~26	NR	NR	OR	3.07 (2.15 to 4.38)	NR
	Agomelatine	Dropout due to AE	All	Placebo	8	~23	NR	NR	OR	1.21 (0.94 to 1.56)	NR

*Evidence is based on RCTs unless specified otherwise.

Abbreviations: AE = adverse event; CG = control group; CI = confidence interval; ES = effect size; IG = intervention group; NR = not reported; OR = odds ratio; RR = relative risk; SSRI = selective serotonin reuptake inhibitor.

Appendix E Table 34. Results for Any Serious Adverse Events From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	Followup	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Viswanathan, 2021[107]	Pharm	Serious AEs	Perinatal	Any	NR	NR	NR	NR	NR	NR	NR
Jakobsen, 2017[109]	SSRI	Serious AEs	All	Placebo	Post-tx	44	239/8,242 (2.7)	106/4,956 (2.1)	OR	1.39 (1.12 to 1.72)	0.0
Sobieraj, 2019[126]	Citalopram	Serious AEs	Older	Placebo	48+	1	11/61 (18.0)	5/61 (8.2)	RR	2.20 (-0.81 to 5.96)	NR
	Duloxetine	Serious AEs	Older	Placebo	12+	2	2/358 (5.6)	7/249 (2.8)	RR	0.20 (0.04 to 0.97)	NR
	Duloxetine	Serious AEs	Older	Placebo	2-48	1	13/249 (5.2)	4/121 (3.3)	RR	1.58 (0.53 to 4.74)	NR
	Vortioxetine	Serious AEs	Older	Placebo	12+	1	1/156 (0.6)	4/145 (2.8)	RR	0.23 (0.03 to 2.05)	NR
	Bupropion	Serious AEs	Older	Placebo	12+	1	2/211 (0.9)	7/207 (3.4)	RR	0.28 (0.06 to 1.33)	NR

*Evidence is based on RCTs unless specified otherwise.

Abbreviations: AE = adverse event; CG = control group; CI = confidence interval; ES = effect size; IG = intervention group; NR = not reported; OR = odds ratio; RR = relative risk; SSRI = selective serotonin reuptake inhibitor.

Appendix E Table 35. Results for Suicide-Related Outcomes From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	FUP, wks	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Braun, 2016[115]	AD	Suicide deaths	All	Placebo	12+	29	7/ (2.18) (0.87, 4.48)	1/ (0.43) (0.006, 2.41)	RR	5.03 (0.78 to 114.1)	NR
Kaminski, 2020[120]	2nd gen	Suicide deaths	All	Placebo	Post-tx	NR	37/31,781 (0.12)	4/10,080 (0.04)	OR	1.74 (0.78 to 3.90)	NR
Jakobsen, 2017[109]	SSRI	Suicide deaths	All	Placebo	Post-tx	6	3/ (NR)	4/ (NR)	RR	0.68 (0.16 to 2.81)	NR
KoKoAung, 2015[122]	SSRI	Suicide deaths (Cohort studies)	Older	No SSRI prescription	NR	2	NR	NR	NR	NR	NR
Braun, 2016[115]	AD	Suicide attempts	All	Placebo	12+	25	13/ (4.34) (2.31, 7.42)	1/ (0.48) (0.006, 2.67)	RR	9.02 (1.58 to 193.6)	NR
Kaminski, 2020[120]	2nd gen	Suicide attempts	All	Placebo	Post-tx	NR	206/31,781 (0.7)	28/10,080 (0.3)	OR	1.53 (1.09 to 2.15)	NR
Jakobsen, 2017[109]	SSRI	Suicide attempts	All	Placebo	Post-tx	8	16/ (NR)	5/ (NR)	RR	1.76 (0.59 to 5.22)	NR
KoKoAung, 2015[122]	SSRI	Suicide attempts	Older	Placebo	6-9	4	2/293 (0.7)	2/299 (0.7)	OR	1.00 (0.14 to 7.10)	23
	SSRI	Suicide attempts (Cohort studies)	Older	No SSRI prescription	NR	3	NR	NR	NR	NR	NR
Hengartner, 2021[110]	2nd gen	Suicide death or attempt (Obs studies)	All	No AD	NR	27	NR	NR	RR	1.29 (1.06 to 1.57)	95
	2nd gen	Suicide death or attempt (Obs,	All	No AD	NR	51	NR	NR	RR	1.40 (1.19 to 1.65)	94.1

Appendix E Table 35. Results for Suicide-Related Outcomes From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	FUP, wks	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
		covariate adj)									
	2nd gen	Suicide death or attempt (Obs, no covar adj)	All	No AD	NR	10	NR	NR	RR	1.71 (0.96 to 3.04)	97.2
	2nd gen	Suicide death or attempt (Obs, financial COI)	All	No AD	NR	28	NR	NR	RR	0.96 (0.82 to 1.12)	86.1
	2nd gen	Suicide death or attempt (Obs, no financial COI)	All	No AD	NR	33	NR	NR	RR	2.02 (1.66 to 2.46)	94.3
Hengartner, 2021[110] continued	2nd gen	Suicide death or attempt (Obs, oth country)	All	No AD	NR	4	NR	NR	RR	1.73 (0.84 to 3.57)	10.8
	2nd gen	Suicide death or attempt (Obs, Europe)	All	No AD	NR	36	NR	NR	RR	1.82 (1.51 to 2.20)	95.7
	2nd gen	Suicide death or attempt (Obs, N Am)	All	No AD	NR	21	NR	NR	RR	0.82 (0.68 to 0.99)	65.5
	2nd gen	Suicide death or attempt (Obs, high RoB)	All	No AD	NR	12	NR	NR	RR	1.92 (1.21 to 3.03)	96.5
	2nd gen	Suicide death or attempt (Obs, low RoB)	All	No AD	NR	49	NR	NR	RR	1.36 (1.15 to 1.61)	94.4
	2nd gen	Suicide death or attempt (Case-control)	All	No AD	NR	24	NR	NR	RR	1.22 (1.00 to 1.50)	79.7
	2nd gen	Suicide death	All	No AD	NR	37	NR	NR	RR	1.59	96.4

Appendix E Table 35. Results for Suicide-Related Outcomes From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	FUP, wks	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
		or attempt (Cohort)								(1.27 to 1.99)	
Hengartner, 2021[110]	2nd gen	Suicide death or attempt (Obs studies)	Any dx	No AD	NR	20	NR	NR	RR	1.65 (1.26 to 2.17)	93.1
	2nd gen	Suicide death or attempt (Obs studies)	Older	No AD	NR	4	NR	NR	RR	1.67 (0.35 to 7.86)	94.7
	2nd gen	Suicide death or attempt (Obs studies)	Not older (<65 years)	No AD	NR	54	NR	NR	RR	1.44 (1.21 to 1.71)	95.0
	2nd gen	Suicide death or attempt (Obs studies)	MDD dx	No AD	NR	41	NR	NR	RR	1.35 (1.10 to 1.65)	95.6
	SSRI	Suicide death or attempt (Obs studies)	All	No AD	NR	19	NR	NR	RR	1.19 (0.88 to 1.60)	96.0
	SNA	Suicide death or attempt (Obs studies)	All	No AD	NR	21	NR	NR	RR	1.28 (0.90 to 1.80)	96.2
	Any 2nd gen	Suicide death or attempt (Obs studies)	All	No AD	NR	21	NR	NR	RR	1.87 (1.55 to 2.25)	89.3
Gibbons, 2012[117]	AD	Suicidal ideation	All	Placebo	9	NR	NR	NR	NR	NR	NR
Jakobsen, 2017[109]	SSRI	Suicidal ideation	All	Placebo	Post-tx	11	NR	NR	RR	0.80 (0.36 to 1.77)	NR
KoKoAung, 2015[122]	SSRI	Suicidal ideation	Older	Placebo	6-9	2	3/634 (0.5)	6/647 (0.9)	OR	0.52 (0.14 to 1.94)	0
Naslund, 2018[108]	SSRI	Suicidality	All	Placebo	1-6	NR	NR	NR	NR	NR	NR

*Evidence is based on RCTs unless specified otherwise.

Appendix E Table 35. Results for Suicide-Related Outcomes From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Abbreviations: AD = antidepressant; AE = adverse event; CG = control group; CI = confidence interval; ES = effect size; FUP = followup; IG = intervention group; NR = not reported; OR = odds ratio; RoB = risk of bias; RR = relative risk; SSRI = selective serotonin reuptake inhibitor; tx = treatment.

Appendix E Table 36. Results for Falls and Fractures From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	FUP, wks	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Sobieraj, 2019[126]	SSRI	Falls (Cohort study)	Older	No AD	NR	1	NR	NR	HR	1.66 (1.58 to 1.73)	NR
Khanassov, 2018[121]	SSRI or SNRI	Falls (Cohort studies)	All	No SSRI or SNRI	NR	3	NR	NR	RR	1.66 (1.59 to 1.74)	0
Sobieraj, 2019[126]	SNRI	Falls	Older	Placebo	12+	1	45/456 (10)	15/225 (7)	RR	1.46 (0.84 to 2.55)	0
	Duloxetine	Falls	Older	Placebo	2-48	1	59/249 (23.7)	17/121 (14)	RR	1.69 (1.03 to 2.76)	NR
	Duloxetine	Falls	Older	Placebo	12+	2	45/456 (9.9)	15/225 (6.7)	RR	1.46 (0.84 to 2.55)	NR
	Venlafaxine	Falls (Cohort study)	Older	No AD	NR	1	NR	NR	HR	1.67 (1.48 to 1.88)	NR
	Mirtazapine	Falls (Cohort study)	Older	No AD	NR	1	NR	NR	HR	1.18 (1.04 to 1.36)	NR
	Trazadone	Falls (Cohort study)	Older	No AD	NR	1	NR	NR	HR	1.54 (1.28 to 1.87)	NR
	SSRI	Fractures (Cohort study)	Older	No AD	NR	1	NR	NR	HR	1.58 (1.48 to 1.68)	NR
Khanassov, 2018[121]	SSRI	Fractures (Observational studies controlling for depression)	All	No SSRI	NR	10	NR	NR	RR	1.62 (1.39 to 1.90)	87.9
	SSRI	Fractures (Observational studies)	All	No SSRI	NR	23	NR	NR	RR	1.67 (1.56 to 1.79)	88.4
	SSRI	Fractures (Observational studies not controlling for depression)	All	No SSRI	NR	12	NR	NR	RR	1.73 (1.60 to 1.87)	86.5
	SNRI	Fractures (Observational studies)	All	NR	NR	NR	NR	NR	NR	NR	NR

Appendix E Table 36. Results for Falls and Fractures From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	FUP, wks	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Sobieraj, 2019[126]	Duloxetine	Fractures	Older	Placebo	12+	1	0/156 (0)	1/145 (0.7)	RD	-0.007 (-0.04 to 0.02)	NR
	Venlafaxine	Fractures (Cohort study)	Older	No AD	NR	1	NR	NR	HR	1.85 (1.58 to 2.18)	NR
	Vortioxetine	Fractures	Older	Placebo	12+	1	0/156 (0)	1/145 (0.7)	RD	-0.01 (-0.04 to 0.02)	NR
	Mirtazapine	Fractures (Cohort study)	Older	No AD	NR	1	NR	NR	HR	1.44 (1.23 to 1.73)	NR
	Trazadone	Fractures (Cohort study)	Older	No AD	NR	1	NR	NR	HR	0.95 (0.70 to 1.35)	NR
	Duloxetine	Hip fracture	Older	Placebo	2-48	1	1/249 (0.4)	0/121 (0)	RD	0.002 (-0.03 to 0.02)	NR
	Duloxetine	Ankle fracture	Older	Placebo	2-48	1	1/249 (0.4)	0/121 (0)	RD	0.002 (-0.03 to 0.02)	NR

*Evidence is based on RCTs unless specified otherwise.

Abbreviations: AD = antidepressant; CG = control group; CI = confidence interval; ES = effect size; FUP = followup; HR = hazard ratio; IG = intervention group; NR = not reported; RD = risk difference; RR = relative risk; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; tx = treatment.

Appendix E Table 37. Results for CVD-Related Outcomes From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	FUP, wks	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Maslej, 2017[124]	AD	CVD events (Cohort + RCT)	All	No AD	NR	NR	NR	NR	HR	1.05 (0.92 to 1.20)	26
	AD	CVD events (Cohort + RCT)	General	No AD	NR	NR	NR	NR	HR	1.14 (1.08 to 1.21)	NR
	AD	CVD events (Cohort + RCT)	CVD pts	No AD	NR	NR	NR	NR	HR	0.93 (0.82 to 1.06)	NR
	SSRI or SNRI	CVD events (Cohort + RCT)	All	No AD	NR	NR	NR	NR	HR	1.05 (0.90 to 1.24)	NR
	TCA	CVD events (Cohort studies)	All	No AD	NR	NR	NR	NR	HR	0.99 (0.83 to 1.18)	NR
	Oth 2nd gen	CVD events (Cohort + RCT)	All	No AD	NR	NR	NR	NR	HR	1.06 (0.87 to 1.29)	NR
Trajkova, 2019[127]	AD	Stroke (Cohort studies, pts with MDD)	All	No AD	NR	5	NR	NR	RR	1.33 (1.12 to 1.55)	88.0
	AD	Stroke (Obs studies)	All	No AD	NR	16	NR	NR	RR	1.41 (1.13 to 1.69)	93.7
	AD	Stroke (Obs studies, adj for MDD)	All	No AD	NR	NR	NR	NR	RR	1.23 (1.07 to 1.39)	58.1
	SSRI	Stroke (Obs studies, adj for MDD)	All	No SSRI	NR	NR	NR	NR	RR	1.27 (1.07 to 1.47)	77.1
	SSRI	Stroke (Obs studies, pts with MDD)	All	No SSRI	NR	6	NR	NR	RR	1.27 (1.11 to 1.43)	76.6
	SSRI	Stroke (Obs studies)	All	No SSRI	NR	16	NR	NR	RR	1.41 (1.13 to 1.69)	94.5
	TCA	Stroke (Obs studies, pts with MDD)	All	No TCA	NR	5	NR	NR	RR	1.21 (1.02 to 1.40)	47.3
	TCA	Stroke (Obs studies)	All	No TCA	NR	9	NR	NR	RR	1.08 (0.93 to 1.22)	0
	TCA	Stroke (Cohort studies, adjusted	All	No TCA	NR	2	NR	NR	RR	1.20 (0.88 to 1.52)	0

Appendix E Table 37. Results for CVD-Related Outcomes From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	FUP, wks	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
		for MDD)									
Jensen, 2019[119]	SSRI	Intracranial hemorrhage (Obs studies, recurrent ICrH)	All	No SSRI	NR	3	NR	NR	RR	0.95 (0.83 to 1.09)	0.0
	SSRI	Intracranial hemorrhage (Obs studies, 1st ICrH)	All	No SSRI	NR	24	NR	NR	RR	1.31 (1.15 to 1.48)	75.4
	SSRI	Intracranial hemorrhage (Obs studies)	All	No SSRI	NR	27	NR	NR	RR	1.26 (1.11 to 1.42)	76.1
Kunutsor, 2018[123]	AD	Venous thromboembolism (Obs studies)	All	No AD	0.9-13.5y	6	NR	NR	RR	1.27 (1.06 to 1.51)	79
	SSRI	Venous thromboembolism (Obs studies)	All	No AD	0.9-13.5y	4	NR	NR	RR	1.12 (1.02 to 1.23)	NR
	TCA	Venous thromboembolism (Obs studies)	All	No AD	0.9-13.5y	4	NR	NR	RR	1.16 (1.06 to 1.27)	NR
	Oth 2nd gen	Venous thromboembolism (Obs studies)	All	No AD	0.9-13.5y	4	NR	NR	RR	1.59 (1.21 to 2.09)	NR
Sobieraj, 2019[126]	Duloxetine	Arrhythmia	Older	Placebo	2-48	3	1/249 (0.4)	0/121 (0)	RD	0.002 (-0.03 to 0.02)	NR
	Bupropion	Arrhythmia	Older	Placebo	12+	1	0/211 (0)	1/207 (0.5)	RD	-0.01 (-0.03 to 0.02)	NR

*Evidence is based on RCTs unless specified otherwise.

Abbreviations: AD = antidepressant; CG = control group; CI = confidence interval; CVD = cardiovascular disease; ES = effect size; FUP = followup; HR = hazard ratio; IG = intervention group; MDD = major depressive disorder; NR = not reported; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Appendix E Table 38. Results for Mortality From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	Followup	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Maslej, 2017[124]	AD	Mortality (Cohort + RCT)	All	No AD	NR	16	NR	NR	HR	1.09 (0.92 to 1.29)	87
	AD	Mortality (Cohort + RCT)	General	No AD	NR	10	NR	NR	HR	1.33 (1.14 to 1.55)	NR
	AD	Mortality (Cohort + RCT)	CVD pts	No AD	NR	10	NR	NR	HR	0.90 (0.76 to 1.07)	NR
Sobieraj, 2019[126]	SSRI	Mortality (Cohort study)	Older	No AD	NR	1	NR	NR	HR	1.54 (1.48 to 1.59)	NR
	Citalopram	Mortality	Older	Placebo	48+	1	0/60 (0)	1/61 (1.6)	RD	0.02 (-0.05 to 0.09)	NR
	Escitalopram	Mortality	Older	Placebo	12+	1	1/173 (0.6)	1/180 (0.6)	RD	0.00 (-0.046 to 0.027)	NR
	Fluoxetine	Mortality	Older	Placebo	12+	1	0/164 (0)	1/180 (0.6)	RD	-0.01 (-0.05 to 0.02)	NR
Maslej, 2017[124]	SSRI or SNRI	Mortality (Cohort + RCT)	All	No AD	NR	NR	NR	NR	HR	1.06 (0.85 to 1.32)	NR
Sobieraj, 2019[126]	Duloxetine	Mortality	Older	Placebo	2-48	1	0/249 (0)	0/121 (0)	RR	NA (NR)	NR
	Duloxetine	Mortality	Older	Placebo	12+	2	0/456 (0)	0/225 (0)	RR	NA (NR)	NR
	Venlafaxine	Mortality (Cohort study)	Older	No AD	NR	1	NR	NR	HR	1.65 (1.50 to 1.82)	NR
	Bupropion	Mortality	Older	Placebo	12+	1	0/211 (0)	0/207 (0)	RR	NA (NR)	NA
	Mirtazapine	Mortality (Cohort study)	Older	No AD	NR	1	NR	NR	HR	1.75 (1.61 to 1.91)	NR
Maslej, 2017[124]	TCA	Mortality (Cohort studies)	All	No AD	NR	NR	NR	NR	HR	0.96 (0.75 to 1.24)	NR
Sobieraj, 2019[126]	Trazadone	Mortality (Cohort study)	Older	No AD	NR	1	NR	NR	HR	1.82 (1.60 to 2.08)	NR
Maslej, 2017[124]	Oth 2nd gen	Mortality (Cohort studies)	All	No AD	NR	NR	NR	NR	HR	1.30 (0.99 to 1.70)	NR

*Evidence is based on RCTs unless specified otherwise.

Appendix E Table 38. Results for Mortality From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Abbreviations: AD = antidepressant; CG = control group; CI = confidence interval; ES = effect size; HR = hazard ratio; IG = intervention group; MDD = major depressive disorder; NR = not reported; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Appendix E Table 39. Results for Other Adverse Events From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	FUP, wks	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)	Narrative Summary
Balasubramaniam, 2019[130]	AD	Tolerability	Older	Any		NR	NR	NR	NR	NR	NR	In 5 of 8 trials of escitalopram, citalopram, duloxetine, or venlafaxine compared with a control group, most reported increased side effects with medication; most common side effects were GI-related, fatigue/sedation, and sleep-related.
Na, 2018[125]	Mirtazapine	GI Bleeding (Case-control)	All	No AD	7-180 days	4	NR	NR	OR	1.17 (1.01 to 1.37)	NR	3 of 4 studies showed insufficient quality.
	Mirtazapine	Bleeding (NOS) (Case-control)	All	No AD	7-180 days	4	NR	NR	OR	1.12 (0.97 to 1.29)	NR	3 of 4 studies showed insufficient quality.
Chan, 2019[116]	AD	Dementia (Obs studies)	MDD dx	No AD	NR	4	NR	NR	RR	1.37 (1.11 to 1.70)	0	NR
Gumusoglu, 2022[118]	SSRI	Preeclampsia (Obs studies)	Pregnant	No SSRI	NR	9	NR	NR	OR	1.43 (1.15 to 1.78)	88	Studies were confounded and limited by high heterogeneity and significant

Appendix E Table 39. Results for Other Adverse Events From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	FUP, wks	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)	Narrative Summary
												asymmetry for outcomes of interest. Findings may be due to the relatively small size of cohorts from which study conclusion were drawn. Furthermore, despite evidence for increased preeclampsia risk with SSRIs, most studies do not account for risk factors shared between mood disorders and hypertension or for underlying risk factors shared by depression and preeclampsia.
Wang, 2018[129]	SSRI	Dementia (Obs studies)	Older	Any	3-11yr	5	NR	NR	RR	1.75 (1.03 to 2.96)	98.6	Studies controlled for a number of important confounders, most commonly: age, gender, diabetes, hypertension, stroke, coronary

Appendix E Table 39. Results for Other Adverse Events From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	FUP, wks	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)	Narrative Summary
												artery disease, head injury, anxiety, and depression. Four of the studies reported higher risk ratios with SSRI use, ranging from 1.78 (95% CI, 1.02 to 3.11) to 3.66 (95% CI, 2.62 to 5.10). However, one study reported a statistically significantly lower likelihood of dementia (RR, 0.58 [95% CI, 0.50 to 0.68]), despite covering the same years, within the same geographic region (Taiwan), and controlling for the same confounders as another study that showed an increased risk. Detailed study characteristics

Appendix E Table 39. Results for Other Adverse Events From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	FUP, wks	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)	Narrative Summary
												were not provided to allow an exploration of the differences between the studies that could lead to such strongly differing results.
Wang, 2018[129]	TCA	Dementia (Obs studies)	Older	Any	3-11yr	5	NR	NR	RR	2.13 (1.43 to 3.18)	96	All 4 findings in direction of harm, 3 of 4 statistically significant
Chan, 2019[116]	AD	Mild cognitive impairment	MDD dx	No AD	NR	2	NR	NR	RR	1.20 (1.02 to 1.42)	0	NR
Jacobsen, 2019[111]	Citalopram	Sexual dysfunction	All	Placebo	NR	1	NR	NR	OR	1.32 (0.89 to 1.94)	NA	NR
	Escitalopram	Sexual dysfunction	All	Placebo	NR	1	NR	NR	OR	1.99 (1.18 to 3.34)	NA	NR
	Paroxetine	Sexual dysfunction	All	Placebo	NR	1	NR	NR	OR	1.72 (1.28 to 2.32)	NA	NR
	Desvenlafaxine	Sexual dysfunction	All	Placebo	NR	3	NR	NR	OR	1.02 (0.84 to 1.25)	NR	NR
	Duloxetine	Sexual	All	Placebo	NR	3	NR	NR	OR	1.41	NR	NR

Appendix E Table 39. Results for Other Adverse Events From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome*	Population	Control	FUP, wks	k	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)	Narrative Summary
		dysfunction								(1.15 to 1.74)		
	Vortioxetine	Sexual dysfunction	All	Placebo	NR	6	NR	NR	OR	1.08 (0.88 to 1.32)	NR	NR
	Vilazodone	Sexual dysfunction	All	Placebo	NR	3	NR	NR	OR	1.11 (0.91 to 1.35)	NR	NR
Vlenterie, 2021[128]	AD	Preterm birth	Perinatal	No AD	NR	15	216/ 2116 (10.2)	689/ 8917 (7.7)	OR	1.1 (0.9 to 1.5)	NR	NR
	SSRI	Preterm birth	Perinatal	No SSRI	NR	3	140/ 1,328 (10.5)	468/ 5,652 (8.2)	OR	1.6 (1.0 to 2.5)	NR	NR
	AD	Low birth weight	Perinatal	No AD	NR	14	160/ 2,084 (7.7)	534/ 8,702 (6,1)	OR	0.9 (0.7 to 1.3)	NR	NR
	SSRI	Low birth weight	Perinatal	No SSRI	NR	3	94/ 1,331 (7.1)	409/ 5,726 (7.1)	OR	0.7 (0.5 to 1.1)	NR	NR
	AD	SGA	Perinatal	No AD	NR	8	96/ 1,471 (6.5)	652/ 8,478 (7.7)	OR	0.9 (0.6 to 1.3)	NR	NR
	SSRI	SGA	Perinatal	No SSRI	NR	1	61/953 (6.4)	362/ 4,667 (7.8)	OR	0.8 (0.5 to 1.3)	NR	NR

*Evidence is based on RCTs unless specified otherwise.

Abbreviations: AD = antidepressant; CG = control group; CI = confidence interval; CVD = cardiovascular disease; dx = diagnosis; ES = effect size; FUP = followup; GI = gastrointestinal; HR = hazard ratio; IG = intervention group; MDD = major depressive disorder; NOS = not otherwise specified; NR = not

Appendix E Table 39. Results for Other Adverse Events From ESRs for Pharmacologic Treatment of Depression Compared to Placebo (KQ5)

reported; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

Appendix F Table 1. Intervention Description of Anxiety Screening Studies (KQ1)

Author, Year	IG	Intervention Detail	Adherence	Acceptability
Kroenke, 2018[32]	IG1	The screener was a 5-item scale in which patients rated their sleep, pain, anxiety, depression, and fatigue ("SPADE" symptoms) on a 0-10 scale, which was administered to all patients prior to randomization. Patients who scored ≥4 on any SPADE symptoms were invited to participate in the study. All participants completed the PROMIS, which includes 4 items per SPADE symptom, on a touch-screen tablet. Just before the encounter, clinicians of participants in the intervention group were provided with a printed bar graph of t-scores from the PROMIS for the 5 SPADE symptoms. The PROMIS numeric scores for all five SPADE symptoms were shown on the graph, and elevated scores (T scores ≥55) were further highlighted by including threshold lines and making symptom bars that crossed the threshold line red.	NR	NR
Mathias, 1994[131]	IG1	Physician intervention composed of two parts: 1) Educational demonstration provided to primary care physician by study team physician and 2) a reporting system summarizing the anxiety symptom levels and functional status of the patients enrolled in the study. A study team internist met with each demonstration arm physician to describe the psychometric instruments and their interpretations, explain the patient profile, review results for a minimum of three of their patients, provide educational materials on the management of anxiety, and provide a toll-free telephone number of a study team physician who could answer further questions. Patient profiles, designed to resemble laboratory slips, summarized all self-reported information in a simple format. The demonstration arm physicians received updated patient profiles throughout the course of the study, showing the changes in each patient's scores. No recommendation about treatment of specific patients was made. Instead, decisions regarding whether to provide counseling or medication, refer the patient, or do nothing were left entirely to the physician.	NR	NR

Abbreviations: IG = intervention group; NR = not reported; PROMIS = Patient-Reported Outcomes Measurement Information System.

Appendix F Table 2. Test Accuracy of Screening Instruments to Detect Generalized Anxiety Disorder (KQ2)

Screening Test	Cutoff	Author, year	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
GAD-2	≥1	Nath, 2018[132]	1.0 (0.99, 1.0*)	0.60 (0.60, 0.61*)	0.11 (0.10, 0.12)*	1.0 (1.0, 1.0)*	NR
	≥2	Ahn, 2019[133]	0.93 (0.86, 0.97)	0.69 (0.68, 0.69)	0.20 (0.62, 0.24)	0.99 (0.98, 1.0)	NR
		Kujanpaa, 2014[134]	0.83 (0.36, 0.99)	0.75 (0.67, 0.82)	0.12 (0.05, 0.26)*	0.99 (0.95, 1.0)*	NR
		Spitzer, 2006[20]	0.95 (0.87, 0.98)	0.64 (0.64, 0.67)	0.18 (0.14, 0.22)*	0.99 (0.98, 1.0)*	0.908 (0.876, 0.940)
	≥3	Ahn, 2019[133]	0.76 (0.66, 0.83)	0.88 (0.87, 0.88)	0.34 (0.27, 0.41)	0.98 (0.97, 0.99)	NR
		Kujanpaa, 2014[134]	0.83 (0.36, 0.99)	0.90 (0.84, 0.95)	0.26 (0.12, 0.49)*	0.99 (0.96, 1.0)*	NR
		Nath, 2018[132]	0.69 (0.64, 0.73*)	0.91 (0.90, 0.91*)	0.26 (0.23, 0.28)*	0.98 (0.98, 0.99*)	NR
		Spitzer, 2006[20]	0.86 (0.76, 0.93)	0.83 (0.80, 0.85)	0.29 (0.24, 0.36)*	0.99 (0.98, 0.99)*	0.908 (0.876, 0.940)
	≥4	Ahn, 2019[133]	0.60 (0.50, 0.69)	0.93 (0.92, 0.94)	0.42 (0.34, 0.51)	0.96 (0.95, 0.98)	NR
		Kujanpaa, 2014[134]	0.67 (0.22, 0.96)	0.95 (0.90, 0.98)	0.36 (0.15, 0.65)*	0.99 (0.95, 1.0)*	NR
GAD-7	≥5	Ahn, 2019[133]	0.93 (0.86, 0.97)	0.71 (0.70, 0.71)	0.21 (0.17, 0.25)	0.99 (0.99, 1.0)	NR
		Kujanpaa, 2014[134]	1.0 (0.54, 1.0)	0.73 (0.65, 0.80)	0.13 (0.06, 0.26)*	1.0 (0.96, 1.0)*	NR
		Spitzer, 2006[20]	0.97 (0.90, 1.0)	0.57 (0.53, 0.60)	0.16 (0.13, 0.19)*	1.0 (0.99, 1.0)*	0.905 (0.872, 0.938)
	≥6	Ahn, 2019[133]	0.90 (0.82, 0.95)	0.76 (0.76, 0.77)	0.24 (0.20, 0.25)	0.99 (0.98, 1.0)	NR
		Kujanpaa, 2014[134]	1.0 (0.54, 1.0)	0.79 (0.72, 0.86)	0.17 (0.08, 0.32)*	1.0 (0.97, 1.0)*	NR
		Spitzer, 2006[20]	0.95 (0.87, 0.98)	0.65 (0.61, 0.67)	0.18 (0.15, 0.22)*	0.99 (0.98, 1.0)*	0.905 (0.872, 0.938)
	≥7	Ahn, 2019[133]	0.87 (0.78, 0.92)	0.81 (0.80, 0.82)	0.28 (0.23, 0.33)	0.99 (0.98, 0.99)	NR
		Kujanpaa, 2014[134]	1.0 (0.54, 1.0)	0.83 (0.75, 0.88)	0.19 (0.09, 0.36)*	1.0 (0.97, 1.0)*	NR
		Spitzer, 2006[20]	0.95	0.70	0.20	0.99	0.905

Appendix F Table 2. Test Accuracy of Screening Instruments to Detect Generalized Anxiety Disorder (KQ2)

Screening Test	Cutoff	Author, year	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
			(0.87, 0.98)*	(0.67, 0.73)*	(0.17, 0.25)*	(0.98, 1.0)*	(0.872, 0.938)
	≥8	Ahn, 2019[133]	0.81 (0.72, 0.99)	0.84 (0.84, 0.85)	0.31 (0.25, 0.36)	0.98 (0.97, 0.99)	NR
		Kujanpaa, 2014[134]	0.83 (0.36, 0.99)	0.88 (0.82, 0.93)	0.23 (0.10, 0.43)*	0.99 (0.96, 1.0)*	NR
		Spitzer, 2006[20]	0.92 (0.83, 0.96)*	0.76 (0.73, 0.79*)	0.24 (0.19, 0.09)*	0.99 (0.96, 1.0)*	0.905 (0.872, 0.938)
	≥9	Ahn, 2019[133]	0.78 (0.68, 0.85)	0.87 (0.86, 0.88)	0.34 (0.27, 0.40)	0.98 (0.97, 0.99)	NR
		Kujanpaa, 2014[134]	0.83 (0.36, 0.99)	0.94 (0.89, 0.97)	0.36 (0.16, 0.61)*	0.99 (0.96, 1.0)*	NR
		Spitzer, 2006[20]	0.90 (0.82, 0.95)*	0.79 (0.76, 0.82*)	0.26 (0.21, 0.32)*	0.99 (0.98, 1.0)*	0.905 (0.872, 0.938)
	≥10	Ahn, 2019[133]	0.72 (0.62, 0.80)	0.89 (0.88, 0.90)	0.36 (0.29, 0.43)	0.97 (0.96, 0.98)	NR
		Kujanpaa, 2014[134]	0.67 (0.22, 0.96)	0.95 (0.90, 0.98)	0.36 (0.15, 0.65)*	0.99 (0.95, 1.0)*	NR
		Spitzer, 2006[20]	0.89 (0.80, 0.94)*	0.82 (0.79, 0.84*)	0.29 (0.23, 0.35)*	0.99 (0.98, 0.99)*	0.905 (0.872, 0.938)
	≥11	Ahn, 2019[133]	0.70 (0.60, 0.78)	0.92 (0.91, 0.92)	0.41 (0.34, 0.49)	0.97 (0.96, 0.98)	NR
		Spitzer, 2006[20]	0.82 (0.72,0.89)*	0.85 (0.82, 0.87)*	0.31 (0.25, 0.38)*	0.98 (0.97, 0.99)*	0.905 (0.872, 0.938)
	≥12	Spitzer, 2006[20]	0.73 (0.61, 0.82)*	0.89 (0.87, 0.91)*	0.35 (0.28, 0.43)*	0.98 (0.96, 0.98)*	0.905 (0.872, 0.938)
	≥13	Spitzer, 2006[20]	0.66 (0.54, 0.76)*	0.91 (0.89, 0.93)*	0.38 (0.30, 0.46)*	0.97 (0.96, 0.98)*	0.906 (NR)
	≥14	Spitzer, 2006[20]	0.56 (0.45, 0.67)*	0.92 (0.90, 0.94)*	0.37 (0.28, 0.46)*	0.96 (0.95, 0.97)*	0.905 (0.872, 0.938)
	≥15	Spitzer, 2006[20]	0.48 (0.37, 0.59)*	0.95 (0.93, 0.96)*	0.42 (0.32, 0.52)*	0.96 (0.94, 0.97)*	0.905 (0.872, 0.938)

*Calculated.

Abbreviations: AUC = area under curve; CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale; GAD = generalized anxiety disorder; GAS = Geriatric Anxiety Scale; NR = not reported; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; SE = standard error.

Appendix F Table 3. Test Accuracy of Screening Instruments to Detect Any Anxiety Disorder (KQ2)

Screening Test	Cutoff	Author, Year	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
GAD-2	≥1	Ahn, 2019[133]	0.83 (0.78, 0.87)	0.55 (0.53, 0.56)	0.30 (0.26, 0.34)	0.93 (0.91, 0.95)	NR
		Austin, 2021[135]	0.90 (0.74, 0.96)*	0.63 (0.59, 0.66)*	0.07 (0.05, 0.10)*	0.99 (0.98, 1.0)*	0.834
		Nath, 2018[132]	0.70 (0.68, 0.73)*	0.64 (0.63, 0.65)*	0.27 (0.26, 0.29)*	0.92 (0.91, 0.93)*	NR
	≥2	Ahn, 2019[133]	0.74 (0.69, 0.79)	0.73 (0.71, 0.74)	0.39 (0.34, 0.43)	0.92 (0.90, 0.94)	NR
		Austin, 2021[135]	0.70 (0.52, 0.83)*	0.82 (0.80, 0.85)*	0.11 (0.08, 0.17)*	0.99 (0.98, 0.99)*	0.834
		Kujanpaa, 2014[134]	0.62 (0.43,0.78)*	0.80 (0.72, 0.86)*	0.39 (0.26, 0.54)*	0.91 (0.84, 0.95)*	NR
		Spitzer, 2006[20]	0.86 (0.80, 0.90)	0.70 (0.67, 0.74)	0.41 (0.36, 0.46)*	0.95 (0.93, 0.97)*	0.853 (0.823, 0.883)
	≥3	Ahn, 2019[133]	0.50 (0.44, 0.55)	0.90 (0.89, 0.91)	0.54 (0.47, 0.61)	0.88 (0.86, 0.90)	NR
		Austin, 2021[135]	0.30 (0.17, 0.48*)	0.98 (0.96, 0.98*)	0.27 (0.16, 0.45*)	0.98 (0.96, 0.98*)	0.834
		Kujanpaa, 2014[134]	0.38 (0.22, 0.57)*	0.93 (0.87, 0.96)*	0.53 (0.32, 0.73)*	0.88 (0.81, 0.92)*	NR
		Nath, 2018[132]	0.26 (0.24, 0.29*)	0.91 (0.90, 0.92*)	0.36 (0.33, 0.39*)	0.87 (0.86, 0.87*)	NR
		Spitzer, 2006[20]	0.65 (0.57, 0.71)	0.88 (0.85, 0.90)	0.57 (0.50, 0.63)*	0.91 (0.89, 0.93)*	0.853 (0.823, 0.883)
	≥4	Kujanpaa, 2014[134]	0.27 (0.14, 0.46)*	0.97 (0.92, 0.99)*	0.64 (0.35, 0.85)*	0.86 (0.80, 0.91)*	NR
GAD-7	≥1	Makulowich, 2018[136]	0.94 (0.70, 1.0)	0.47 (0.30, 0.65)	0.50 (0.42, 0.58)	0.93 (0.66, 0.99)	0.80 (0.67, 0.90)
	≥2	Makulowich, 2018[136]	0.88 (0.62, 0.98)	0.59 (0.41, 0.75)	0.54 (0.43, 0.65)	0.89 (0.69, 0.97)	0.80 (0.67, 0.90)
		Vasiliadis, 2015[137]	0.92 (0.88, 0.95)*	0.25 (0.23, 0.27)*	0.17 (0.15, 0.20)*	0.95 (0.92, 0.97)*	0.695 (NR)
	≥3	Makulowich, 2018[136]	0.69 (0.42, 0.89)	0.71 (0.52, 0.85)	0.57 (0.42, 0.71)	0.80 (0.65, 0.90)	0.80 (0.67, 0.90)
		Vasiliadis, 2015[137]	0.87 (0.82, 0.90)*	0.35 (0.33, 0.37)*	0.19 (0.17, 0.21)*	0.94 (0.92, 0.96)*	0.695 (NR)
	≥4	Ahn, 2019[133]	0.78	0.66	0.35	0.93	NR

Appendix F Table 3. Test Accuracy of Screening Instruments to Detect Any Anxiety Disorder (KQ2)

Screening Test	Cutoff	Author, Year	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
			(0.72, 0.83)	(0.65, 0.68)	(0.31, 0.39)	(0.91, 0.95)	
		Austin, 2021[135]	0.80 (0.63, 0.90)*	0.71 (0.68, 0.73)*	0.08 (0.06, 0.12)*	0.99 (0.98, 1.0*)	0.818 (NR)
		Makulowich, 2018[136]	0.62 (0.35, 0.85)	0.88 (0.72, 0.97)	0.75 (0.52, 0.89)	0.81 (0.69, 0.89)	0.80 (0.67, 0.90)
		Vasiliadis, 2015[137]	0.80 (0.75, 0.85)*	0.46 (0.43, 0.49)*	0.20 (0.18, 0.23)*	0.93 (0.91, 0.95)*	0.695 (NR)
	≥5	Ahn, 2019[133] 4849	0.72 (0.67, 0.78)	0.74 (0.73, 0.76)	0.40 (0.35, 0.44)	0.92 (0.90, 0.94)	NR
		Austin, 2021[135]	0.67 (0.49, 0.81)*	0.80 (0.77, 0.82)*	0.10 (0.06, 0.14)*	0.99 (0.98, 0.99)*	0.818 (NR)
GAD-7 continued		Kujanpaa, 2014[134]	0.81 (0.62, 0.91)*	0.81 (0.73, 0.87)*	0.47 (0.33, 0.61)*	0.95 (0.89, 0.98)*	NR
		Spitzer, 2006[20]	0.90 (0.85, 0.94)	0.63 (0.60, 0.66)	0.37 (0.33, 0.42)*	0.96 (0.94, 0.98)*	0.864 (0.835, 0.892)
		Vasiliadis, 2015[137]	0.71 (0.65, 0.76)*	0.57 (0.54, 0.59)*	0.22 (0.19, 0.25)*	0.92 (0.90, 0.94)*	0.695 (NR)
	≥6	Ahn, 2019[133]	0.66 (0.60, 0.72)	0.80 (0.78, 0.81)	0.43 (0.38, 0.49)	0.91 (0.89, 0.93)	NR
		Austin, 2021[135]	0.57 (0.39, 0.73)*	0.87 (0.84, 0.89)*	0.12 (0.08, 0.19)*	0.98 (0.97, 0.99)*	0.818 (NR)
		Kujanpaa, 2014[134]	0.77 (0.58, 0.89)*	0.87 (0.80, 0.92)*	0.56 (0.40, 0.70)*	0.95 (0.89, 0.98)*	NR
		Makulowich, 2018[136]	0.38 (0.16, 0.65)	0.91 (0.76, 0.98)	0.70 (0.41, 0.89)	0.72 (0.64, 0.79)	0.80 (0.67, 0.90)
		Spitzer, 2006[20]	0.85 (0.79, 0.90)	0.71 (0.68, 0.74)	0.42 (0.37, 0.47)*	0.95 (0.93, 0.97)*	0.864 (0.835, 0.892)
		Vasiliadis, 2015[137]	0.56 (0.50, 0.62)*	0.70 (0.68, 0.72)*	0.24 (0.21, 0.28)*	0.90 (0.88, 0.92)*	0.695 (NR)
	≥7	Ahn, 2019[133]	0.61 (0.55, 0.66)	0.84 (0.83, 0.86)	0.47 (0.41, 0.53)	0.90 (0.88, 0.92)	NR
		Austin, 2021[135]	0.43 (0.27, 0.61)*	0.93 (0.91, 0.94)*	0.16 (0.10, 0.26)*	0.98 (0.97, 0.99)*	0.818 (NR)
		Kujanpaa, 2014[134]	0.69 (0.50, 0.83)*	0.90 (0.83, 0.94)*	0.58 (0.41, 0.74)*	0.93 (0.87, 0.97)*	NR
		Makulowich, 2018[136]	0.31 (0.11, 0.59)	0.94 (0.80, 0.99)	0.75 (0.39, 0.93)	0.71 (0.63, 0.77)	0.80 (0.67, 0.90)

Appendix F Table 3. Test Accuracy of Screening Instruments to Detect Any Anxiety Disorder (KQ2)

Screening Test	Cutoff	Author, Year	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
		Spitzer, 2006[20]	0.80 (0.74, 0.86)	0.76 (0.73, 0.79)	0.45 (0.39, 0.50)*	0.94 (0.92, 0.96)*	0.864 (0.835, 0.892)
		Vasiliadis, 2015[137]	0.42 (0.36, 0.48*)	0.83 (0.81, 0.85*)	0.30 (0.25, 0.35)*	0.89 (0.88, 0.91)*	0.695 (NR)
	≥8	Ahn, 2019[133]	0.56 (0.51, 0.62)	0.88 (0.86, 0.89)	0.52 (0.45, 0.58)	0.90 (0.88, 0.92)	NR
		Kujanpaa, 2014[134]	0.54 (0.35, 0.71)*	0.94 (0.88, 0.97)*	0.64 (0.43,0.80)*	0.91 (0.84, 0.95)*	NR
		Spitzer, 2006[20]	0.77 (0.70, 0.82)	0.82 (0.80, 0.85)	0.51 (0.45, 0.57*	0.94 (0.92, 0.95)*	0.864 (0.835, 0.892)
		Vasiliadis, 2015[137]	0.30 (0.25, 0.36)*	0.91 (0.89, 0.92)*	0.36 (0.30, 0.43)*	0.88 (0.87, 0.90)*	0.695 (NR)
	≥9	Kujanpaa, 2014[134]	0.50 (0.32, 0.68)	0.99 (0.96, 1.0)*	0.93 (0.69, 0.99)*	0.90 (0.84, 0.94)*	NR
		Makulowich, 2018[136]	0.25 (0.07, 0.52)	0.94 (0.80, 0.99)	0.70 (0.33, 0.92)	0.69 (0.62, 0.75)	0.80 (0.67, 0.90)
		Spitzer, 2006[20]	0.73 (0.66, 0.80)	0.85 (0.83, 0.88)	0.54 (0.48, 0.60)*	0.93 (0.91, 0.94)*	0.864 (0.835, 0.892)
GAD-7 continued	≥10	Austin, 2021[135]	0.27 (0.14, 0.44)*	0.98 (0.97, 0.99)*	0.33 (0.18, 0.53)*	0.98 (0.96, 0.98)*	0.818 (NR)
		Kujanpaa, 2014[134]	0.42 (0.26, 0.61)*	1.0 (0.97, 1.0)*	1.0 (0.74, 1.0)*	0.89 (0.83, 0.93)*	NR
		Spitzer, 2006[20]	0.68 (0.60, 0.74)	0.88 (0.85, 0.90)	0.58 (0.51, 0.64)*	0.92 (0.90, 0.94)*	0.864 (0.835, 0.892)
	≥13	Makulowich, 2018[136]	0.12 (0.02, 0.38)	0.97 (0.85, 1.0)	0.70 (0.19, 0.96)	0.66 (0.62, 0.70)	0.80 (0.67, 0.90)
	≥14	Makulowich, 2018[136]	0.06 (0.002, 0.30)	1.0 (0.90, 1.0)	1.0 (0.21, 1.0*)	0.66 (0.63, 0.68)	0.80 (0.67, 0.90)
	≥21	Makulowich, 2018[136]	0.00 (0.0, 0.21)	1.0 (0.90, 1.0)	NA	0.64 (0.64, 0.64)	0.80 (0.67, 0.90)
GAS	>9	Gould, 2014[138]	0.60 (0.31, 0.83)*	0.75 (0.66, 0.82)*	0.19 (0.09, 0.36)*	0.95 (0.88, 0.98)*	NR
	>10	Gould, 2014[138]	0.50 (0.24, 0.76)*	0.82 (0.73, 0.88)*	0.22 (0.10, 0.42)*	0.94 (0.87, 0.98)*	NR
	>12	Gould, 2014[138]	0.50 (0.24, 0.76)*	0.83 (0.74, 0.89)*	0.23 (0.10, 0.44)*	0.94 (0.87, 0.98)*	NR
	>13	Gould, 2014[138]	0.50	0.84	0.24	0.94	NR

Appendix F Table 3. Test Accuracy of Screening Instruments to Detect Any Anxiety Disorder (KQ2)

Screening Test	Cutoff	Author, Year	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
			(0.24, 0.76)*	(0.76, 0.90)*	(0.11, 0.45)*	(0.88, 0.98)*	
	>14	Gould, 2014[138]	0.50 (0.24, 0.76)*	0.88 (0.80, 0.93)*	0.29 (0.13, 0.53)*	0.95 (0.88, 0.98)*	NR
	>15	Gould, 2014[138]	0.50 (0.24, 0.76)*	0.89 (0.81, 0.94)*	0.31 (0.14, 0.56)*	0.95 (0.88, 0.98)*	NR
	>16	Gould, 2014[138]	0.40 (0.17, 0.69)*	0.94 (0.88, 0.97)*	0.40 (0.17, 0.69)*	0.94 (0.88, 0.97)*	NR
EPDS - Anxiety Subscale	≥4	Austin, 2021[135]	0.73 (0.56, 0.86)*	0.71 (0.68, 0.74)*	0.07 (0.05, 0.11)*	0.99 (0.98, 0.99)*	0.809
	≥5	Austin, 2021[135]	0.70 (0.52, 0.83)*	0.84 (0.81, 0.86)*	0.12 (0.08, 0.18)*	0.99 (0.98,0.99)*	0.809
		Matthey, 2013[139]	0.54 (0.38, 0.70)	NR	NR	NR	NR
	≥6	Austin, 2021[135]	0.40 (0.24, 0.58)*	0.93 (0.92, 0.95)*	0.16 (0.10, 0.26)*	0.98 (0.97, 0.99)*	0.809

* Calculated.

Abbreviations: AUC = area under curve; CI = confidence interval; GAD = generalized anxiety disorder; GAS = Geriatric Anxiety Scale; EPDS = Edinburgh Postnatal Depression Scale; NR = not reported; NPV = negative predictive value; PPV = positive predictive value; SE = standard error.

Appendix F Table 4. Test Accuracy of Screening Instruments to Detect Panic Disorder (KQ2)

Screening Test	Cutoff	Author, year	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
GAD-2	≥2	Kujanpaa, 2014[134]	0.50 (0.19, 0.81)	0.74 (0.66, 0.81)	0.10 (0.04, 0.21)*	0.95 (0.90, 0.98)*	NR
		Spitzer, 2006[20]	0.91 (0.81, 0.97)	0.63 (0.60, 0.66)	0.15 (0.12, 0.19)*	0.99 (0.98, 1.0)*	0.848 (0.805, 0.891)
	≥3	Kujanpaa, 2014[134]	0.30 (0.07, 0.65)	0.89 (0.82, 0.93)	0.17 (0.06, 0.39)*	0.95 (0.89, 0.97)*	NR
		Spitzer, 2006[20]	0.76 (0.64, 0.85)	0.81 (0.79, 0.84)	0.23 (0.18, 0.29)*	0.98 (0.97, 0.99)*	0.848 (0.805, 0.891)
	≥4	Kujanpaa, 2014[134]	0.20 (0.03, 0.56)	0.94 (0.88, 0.97)	0.20 (0.06, 0.51)*	0.94 (0.89, 0.97)*	NR
GAD-7	≥5	Kujanpaa, 2014[134]	0.70 (0.35, 0.94)	0.73 (0.65, 0.80)	0.16 (0.08, 0.29)*	0.97 (0.93, 0.99)*	NR
		Spitzer, 2006[20]	0.94 (0.85, 0.98)	0.56 (0.53, 0.59)	0.14 (0.11, 0.17)*	0.99 (0.98, 1.0)*	0.847 (0.802, 0.891)
	≥6	Kujanpaa, 2014[134]	0.70 (0.35, 0.93)	0.79 (0.72, 0.86)	0.19 (0.10, 0.35)*	0.97 (0.92, 0.99)*	NR
		Spitzer, 2006[20]	0.88 (0.78, 0.95)	0.64 (0.60, 0.67)	0.15 (0.12, 0.19)*	0.99 (0.97, 0.99)*	0.847 (0.802, 0.891)
	≥7	Kujanpaa, 2014[134]	0.60 (0.26, 0.88)	0.82 (0.75, 0.88)	0.15 (0.07, 0.28)*	0.97 (0.92, 0.99)*	NR
		Spitzer, 2006[20]	0.83 (0.72, 0.91)	0.69 (0.66, 0.72)	0.16 (0.13, 0.21)*	0.98 (0.97, 0.99)*	0.847 (0.802, 0.891)
	≥8	Kujanpaa, 2014[134]	0.40 (0.12, 0.74)	0.87 (0.80, 0.92)	0.18 (0.07, 0.39)*	0.95 (0.90, 0.98)*	NR
		Spitzer, 2006[20]	0.82 (0.70, 0.90)	0.75 (0.72, 0.78)	0.19 (0.15, 0.24)	0.98 (0.97, 0.99)*	0.847 (0.802, 0.891)
	≥9	Kujanpaa, 2014[134]	0.4 (0.12, 0.74)	0.93 (0.87, 0.97)	0.29 (0.12, 0.55)*	0.96 (0.91, 0.98)*	NR
		Spitzer, 2006[20]	0.79 (0.67, 0.88)	0.78 (0.75, 0.80)	0.21 (0.16, 0.26)*	0.98 (0.97, 0.99)*	0.847 (0.802, 0.891)
	≥10	Kujanpaa, 2014[134]	0.40 (0.12, 0.74)	0.95 (0.90, 0.98)	0.36 (0.15, 0.65)*	0.96 (0.91, 0.98)*	NR
		Spitzer, 2006[20]	0.74 (0.62, 0.84)	0.81 (0.78, 0.83)	0.22 (0.17, 0.28)*	0.98 (0.96, 0.99)	0.847 (0.802, 0.891)
PHQ-PD	5**	Spitzer, 1999[15]	0.81 (0.69, 0.93)	0.99 (0.98 1.0)	NR	NR	NR

* Calculated.

** "Yes" to all 5 items.

Abbreviations: AUC = area under curve; CI = confidence interval; GAD = generalized anxiety disorder assessment; NR = not reported; NPV = negative predictive value; PHQ-PD = Patient Health Questionnaire – Panic Disorder; PPV = positive predictive value; SE = standard error.

Appendix F Table 5. Test Accuracy of Screening Instruments to Detect Social Anxiety Disorder (KQ2)

Screening Test	Cutoff	Author, year	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
GAD-2	≥2	Spitzer, 2006[20]	0.85 (0.73, 0.93)	0.62 (0.59, 0.65)	0.13 (0.10, 0.17)*	0.98 (0.97, 0.99)*	0.827 (0.773, 0.881)
	≥3	Spitzer, 2006[20]	0.70 (0.57, 0.81)	0.81 (0.78, 0.83)	0.20 (0.15, 0.25)*	0.98 (0.96, 0.98)*	0.827 (0.773, 0.881)
GAD-7	≥5	Spitzer, 2006[20]	0.88 (0.77, 0.95)	0.55 (0.52, 0.59)	0.12 (0.09, 0.15)*	0.99 (0.97, 0.99)*	0.833 (0.780, 0.886)
	≥6	Spitzer, 2006[20]	0.87 (0.75, 0.94)	0.63 (0.60, .66)	0.13 (0.10, 0.17)*	0.99 (0.97, 0.99)*	0.833 (0.780, 0.886)
	≥7	Spitzer, 2006[20]	0.85 (0.73, .92)	0.69 (0.66, 0.72)	0.15 (0.12, 0.20)*	0.99 (0.97, 0.99)*	0.833 (0.780, 0.886)
	≥8	Spitzer, 2006[20]	0.78 (0.66, 0.88)	0.74 (0.71, 0.77)	0.17 (0.13, 0.21)	0.98 (0.97, 0.99)*	0.833 (0.780, 0.886)
	≥9	Spitzer, 2006[20]	0.77 (0.64, 0.87)	0.77 (0.74, 0.80)	0.18 (0.14, 0.23)*	0.98 (0.97, 0.99)*	0.833 (0.780, 0.886)
	≥10	Spitzer, 2006[20]	0.72 (0.59, 0.83)	0.80 (0.77, 0.83)	0.19 (0.15, 0.25)*	0.98 (0.96, 0.99)*	0.833 (0.780, 0.886)

* Calculated.

Abbreviations: AUC = area under curve; CI = confidence interval; GAD = Generalized Anxiety Disorder assessment; NPV = negative predictive value; PPV = positive predictive value; SE = standard error.

Appendix F Table 6. Detailed Participant Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	BL MH status
Burger, 2020[140]	32.8 (NR)	100 (Pregnant)	High school grad: NR College grad: NR	Employed: NR Single: 8.1 Other SES: SES: Low: 35.1% Moderate: 25.2% High: 39.7%	Black: 4.1 Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	Depressive disorder: 8.2% Anxiety disorder: 30.1% Antidepressants: 1.4%
Clark, 2022[141]	32.2 (18-65)	52	High school grad: 21 College grad: NR	Employed: 76 Single: NR Other SES: NR	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: 88	MDD: 30%
Corpas, 2021[142]	39.6 (18-65)	68.6	<High school grad: 23.8 High school grad: 53.4 College grad: 22.9	Employed: 40 Single: NR Other SES: NR	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	MDD: 81.9%
Fletcher, 2005[143]	39 (16-70)	77	High school grad: NR College grad: 13	Employed: 80 Single: 17 Other SES: NR	Black: 0 Latinx: 0 Asian/AA: 0 Native Am/AN: 0 White: 100	NR
Gensichen, 2019[144]	46.2 (NR)	74	High school grad: NR College grad: NR	Employed: 62.5 Single: NR Other SES: Edu (yrs, median): 10	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	Antidepressants: 54.6%
Graham, 2020[145]	42.3 (18+)	82	High school grad: 9 College grad: 41	Employed: 73 Single: 29 Other SES: Household income (median): $42K; Insurance: 75% private, 18% Medicaid, 13% Medicare	Black: 32 Latinx: 7 Asian/AA: 1 Native Am/AN: 1 White: 65	Screen positive on PHQ-9: 83.6% Screen positive on GAD-7: 89.7%

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Author, Year	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	BL MH status
Kendrick, 2005[146]	35 (18-64)	70	High school grad: NR College grad: NR	Employed: 70 Single: 32 Other SES: NR	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: 96	Depressive disorder: 33.2% Mixed anxiety disorder and depressive disorder, SAD, PD, or agoraphobia: 42.1%
King, 2000[147]	37.5 (18-79)	77.2	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: OPCS Social classes I to III-Non-manual: 70.8%; III-Manual to V: 29.2%	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: 90.8	Depressive disorder: 62.3% Mixed depression and anxiety, PD, or SAD: 34.7% Antidepressants: 0%
Lam, 2010[148]	72 (60+)	58.7	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: 28.9% professional or skilled, 71.1% semi- or un-skilled occupation	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	NR
Lang, 2006[149]	46.6 (18+)	53.2	High school grad: NR College grad: NR	Employed: NR Single: 29 Other SES: Household income: ≤$15,000: 45%; $15,001-30,000: 13%; $30,001-45,000: 19%, >$45,001: 23%	Black: 8 Latinx: 24 Asian/AA: NR Native Am/AN: NR White: 79	MDD: 67.7%
Linden, 2005[150]	43.3 (18-65)	83.3	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: NR	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR	Antidepressants: 0%

Appendix F Table 6. Detailed Participant Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	BL MH status
					White: NR	
Nordgren, 2014[151]	36.5 (19-68)	63	High school grad: 27 College grad: 41	Employed: 47 Single: 29 Other SES: NR	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	NR
O'Mahen, 2022[152]	31.5 (18+)	100 (Pregnant)	High school grad: 11.4 College grad: 30.7	Employed: NR Single: 12.3 Other SES: NR	Black: 4.5 Latinx: 0 Asian/AA: 9.6 Native Am/AN: 0 White: 63.2	GAD-7 7+: 100%
Proudfoot, 2004[153]	43.5 (18-75)	73.7	High school grad: 22.6 College grad: 22.3	Employed: 59.8 Single: 24.8 Other SES: NR	Black: 3.6 Latinx: NR Asian/AA: 1.1 Native Am/AN: NR White: 80.3	Diagnosis of depression: 85.4% Diagnosis of any anxiety disorder: 66.1%
Rollman, 2018[154]	42.7 (18-75)	79.8	High school grad: NR College grad: 47.3	Employed: 69.9 Single: NR Other SES: NR	Black: 16.5 Latinx: NR Asian/AA: NR Native Am/AN: NR White: 81.8	MDD: 84.8% Depression or anxiety med in past year: 77.3%
Roy-Byrne, 2010[155]	43.5 (18-75)	71.1	High school grad: 16.5 College grad: NR	Employed: NR Single: NR Other SES: NR	Black: 11.5 Latinx: 19.5 Asian/AA: NR Native Am/AN: NR White: 56.6	MDD: 64.5%
Schreuders, 2007[156]	52.8 (18+)	70.8	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: Edu Level: Low: 22.3%; Medium: 30%; High: 40%	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	NR
Seekles, 2011[157]	50.6 (18-65)	66.7	High school grad: NR College grad: NR	Employed: 57.4 Single: NR Other SES: NR	Black: NR Latinx: NR Asian/AA: NR	Depressive disorder: 56.5% Any anxiety disorder:

Appendix F Table 6. Detailed Participant Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	BL MH status
					Native Am/AN: NR White: NR	92.6%
Stanley, 2009[158]	66.9 (60+)	78.4	High school grad: NR College grad: NR	Employed: 35.8 Single: 1.49 Other SES: Retired: 55.2%; Widowed: 13.4%	Black: 18.7 Latinx: 8.2 Asian/AA: 2.2 Native Am/AN: NR White: 70.2	Presence of coexistent diagnosis of any depression: 44.8% GAD with or without comorbid depression or other anxiety disorder: 100% Antidepressants: 31%
Stanley, 2014[159]	66.9 (60+)	53.4	High school grad: NR College grad: NR	Employed: 35.4 Single: NR Other SES: Edu (yrs, mean): 15.5; Income: 60K: 26.9%	Black: 17.9 Latinx: 10.8 Asian/AA: 1.4 Native Am/AN: 0.4 White: 78.9	Depressive disorder: 38.6% GAD with or without comorbid depression or other anxiety disorder: 100% Antidepressants: 54.7%
Suchan, 2022[160]	30.8 (18+)	100 (Postpartum)	High school grad: 18 College grad: 33	Employed: 85 Single: 3 Other SES: Family annual income, USD (%): 10K-24,999: 2 25K-49K: 12 50K-74K: 12 75K-99K: 18 100K-149K: 33 150K+: 17	Black: 0 Latinx: 0 Asian/AA: 0 Native Am/AN: 8 White: 85	On psychological medication (NOS): 40%
Sundquist, 2015[161]	41.5 (20-64)	85.4	High school grad: NR College grad: NR	Employed: NR Single: 19.0 Other SES: NR	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	Antidepressants: 35%
Torres-	67.8 (60+)	72.1	High school grad: 37.7	Employed: NR	Black: NR	MDD: 54.1%

Appendix F Table 6. Detailed Participant Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	BL MH status
Platas, 2019[162]			College grad: 33.3	Single: 50.8 Other SES: NR	Latinx: NR Asian/AA: NR Native Am/AN: NR White: 60.7	Anxiety disorder: 57.4% Antidepressants: 45.9% Alcohol consumption: 32.8%
Vera, 2021[163]	40.8 (18-64)	86.7	<High school grad: 29.9 High school grad: NR College grad: NR	Employed: 41.1 Single: NR Other SES: NR	Black: NR Latinx: 100 Asian/AA: NR Native Am/AN: NR White: NR	NR

*Gender was not reported in studies of perinatal patients so participants are counted as women, recognizing that there may be some individuals who do not identify as women; non-binary/gender non-conforming categories were not reported in any studies.

Abbreviations: AA = Asian American; AN = Alaska Native; BL = baseline; GAD = Generalized Anxiety Disorder assessment; MDD = major depressive disorder; MH = mental health; NR = not reported; OPCS = Office of Population Censuses and Surveys; PD = panic disorder; PHQ = Patient Health Questionnaire; SAD = social anxiety disorder; SES = socioeconomic status.

Appendix F Table 7. Detailed Intervention Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations

Author, Year	IG	Intervention detail	Adherence	Acceptability
Burger, 2020[140]	IG1	The treatment protocol consisted of 10-14 individual sessions, of which 6-10 were intended to be delivered during pregnancy. Sessions were scheduled from 20 weeks' gestation up to 3 months postpartum; the exact timing of the sessions was planned on the basis of shared decision making with the participant. The treatment encompassed several optional modules, with evidence-based CBT interventions focusing on the treatment of anxiety disorders (exposure, response prevention and cognitive-challenging work), depressive disorders (additional behavioral activation), or trauma and PTSD (exposure, imagery, and rescripting). In addition, the overall focus was on identifying and changing dysfunctional cognitions and beliefs. Each session also addressed pregnancy-related cognitions and attitudes, and selected evidence-based CBT interventions for specific anxiety and depressive disorders and PTSD were offered. All sessions were structured, explaining the rationale and giving and discussing homework assignments. A treatment manual is available on request.	NR	NR
Clark, 2022[141]	IG1	The protocol allowed up to 14 weekly (90-min) face-to-face therapy sessions and 3 booster sessions in the first 3 months of followup. Several procedures (therapist manual & video illustrations available at www.oxcadatresources.com) were used to reverse maintaining factors identified in Clark and Wells model of social phobia. These include: (a) an individualized version of Clark and Wells model; (b) experiential exercises to demonstrate the adverse effects of self-focused attention and safety behaviors; (c) systematic training in externally focused attention; (d) video feedback for restructuring distorted self-imagery; (e) surveys of other peoples' attitudes to issues (such as blushing) that concern patients; (f) behavioral experiments in which patients test pre-specified negative predictions while dropping their safety behaviors and focusing externally; (g) decatastrophizing exercises; and (h) techniques (discrimination training and memory rescripting) for reducing the impact of early socially traumatic memories. Therapists frequently conducted behavioral experiments in therapy sessions, some of which were outside of the office.	Patients attended 12.8 (SD = 2.1) weekly treatment sessions (18.4 therapist hours) and 2.3 (SD = 0.9) booster sessions (2.8 therapist hours). Total number of within-session behavioral experiments was 13.5 (SD = 6.1)	NR

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Author, Year	IG	Intervention detail	Adherence	Acceptability
Clark, 2022[141]	IG2	In iCT-SAD, all the CT-SAD procedures were delivered within an internet program. The program comprises 8 core modules that patients complete in the first two weeks. Thereafter treatment is personalized with 16 additional modules on specific fearful beliefs or problems being available, depending on patients' concerns. iCT-SAD includes secure video conferencing with recording functionality to support conducting the self-focused attention and safety behavior experiment and video feedback, as well as practicing giving presentations to a virtual audience. Within module video clips illustrate how to set up and conduct behavioral experiments for particular fearful concerns. Patients were encouraged to do several behavioral experiments each week. Therapists scheduled short weekly phone calls with patients to review progress, assign new modules, deepen learning, and plan behavioral experiments. Summaries of calls were sent via the iCT-SAD secure messaging system, which was also used to provide encouragement and suggestions as appropriate. Reminders for behavioral experiments and questionnaire completion could be sent by within program SMS. The core modules were released to all patients.	On average 8.6 (range, 0 to 12) additional modules were released. 81% of released modules were completed. Patients logged into the program for a total of 43.9 hrs (SD = 24.2) and recorded 21.7 (SD = 18.6) completed behavioral experiments. Prior to the 14-week assessment, therapists had a mean of 12.4 (SD, 3.2) short weekly phone calls with their patients (2.8 h in total) and a mean of 2.5 (SD, 1.4) video calls (1.3 h in total), giving a total of 4.1 h of live therapist-patient contact. They sent an average of 38.2 (SD, 22.1) secure messages and 10.7 (SD, 12.2) SMS texts. Total estimated time spent supporting patients was 6.8 h up to week 14, with an additional 1 h during the booster period.	NR
Corpas, 2021[142]	IG1	Brief Group Transdiagnostic Psychotherapy: Experimental treatment that consisted of one session of 1 hour per week for 8 weeks delivered by clinical psychologists in Primary Care centers of Cordoba (Spain). The groups were formed of 8-12 patients per group (10 on average) who were	With the objective of ensuring adherence to the psychological treatment, participants	NR

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Author, Year	IG	Intervention detail	Adherence	Acceptability
		randomly assigned and statistically homogeneous in variables of sociodemographic characteristics. This intervention was designed according to a brief adaptation of the UP for the transdiagnostic approach of emotional disorders (EDs), in which every session corresponds to a different module of the UP. We compressed and selected the more relevant aspects of those modules that originally had more than one session. The UP was developed with the intention that it could be delivered in both individual and group formats, but most of the research conducted to date is focused on an individual format. However, we followed the instructions of previous studies to design our intervention in a group format.	were only allowed to absent themselves to one of the therapeutic sessions to be finally included in the study.	
Fletcher, 2005[143]	IG1	Patients on a waiting list for psychological therapy services were given a pocket-sized self-help manual called "A Handy Guide to Managing Depression and Anxiety: What Should I Do? (Kennedy and Lovell, 2002). Part 1 gives general advice about lifestyle, professional help and treatments available for anxiety and depression. Part 2 uses cognitive behavioral techniques to help the reader identify and change the thoughts and behaviors that lead to negative emotional states. This second part helps the reader to recognize thoughts, physical symptoms, and behavior, and also to identify problems and set goals. The second part also teaches self-help interventions such as behavioral activation, relaxation, problem solving, exposure and cognitive therapy. The patients were given a brief description of the book and advised to read it at their own pace.	Most participants reported that they had read most of the book.	All parts of the book being rated as useful or highly useful by over 50% of the patients (except for "evaluating your progress" for which several patients gave feedback that 12 weeks was too soon to evaluate progress).
Gensichen, 2019[144]	IG1	Intervention group patients received a therapy companion book, providing information about psychoeducation and how to perform the exercises, as well as exposure log sheets. Four structured GP visits were scheduled in a 23-week period; during the first 3 visits, an introduction into the CBT elements was given. Starting from the second GP visit, patients were encouraged to independently perform anxiety exposure exercises at least twice a week. To ensure current symptoms of anxiety are monitored at regular intervals and to enhance treatment adherence, checklist-based telephone monitoring was carried out by a nurse of the GP practice. In case of suboptimal monitoring results, the general practitioners could arrange for additional patient contacts and/or adaptions to be made to the	65% of participants received all 4 sessions, 76% received at least the first 3 sessions, 84% received at least the first 2 sessions, and 9% received 0 sessions.	NR

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Author, Year	IG	Intervention detail	Adherence	Acceptability
		exercise plan.		
Graham, 2020[145]	IG1	The intervention was delivered over 8 weeks using the coach-supported IntelliCare platform. IntelliCare is a suite of mobile apps available on iPhone and Android operating systems. The Hub app organized the user experience by supporting access to clinically focused IntelliCare apps, providing a library of psychoeducational material, and administering a weekly symptom assessment. In this study, participants received access to 5 clinically focused apps. The apps included: (a) Daily Feats: focuses on goal-setting; (b) Day-to-Day: focuses on positive psychology lessons via psychoeducation and prompts; (c) MyMantra: focuses on self-affirmations and personal values; (d) Thought Challenger: focuses on cognitive restructuring/reframing; I WorryKnot: focuses on emotion regulation and anxiety exposure. Each week, a coach recommended a new app to download and try, based on the participant's preferences and a recommendation protocol. Participants were encouraged to try the newly recommended app but could download any app at any time and use or discontinue apps as preferred. Coaching involved an initial 30- to 45-minute engagement phone call to establish goals for mood and anxiety management, ensure the participant can download the Hub app, introduce the suite of available mobile phone apps, build rapport, and set expectations for the coach-participant relationship. Thereafter, participants were to receive 1-2 texts per week from their coach to provide support, offer encouragement, reinforce app use, and check in on progress or challenges. Coaches also responded to all participant-initiated texts within 1 working business day. A 10-minute phone call at week 4 was offered to participants to check in on their experiences with utilization of the program and any relevant concerns with the coaching.	NR	NR
Kendrick, 2005[146]	IG1	Problem solving is a brief structured treatment that helps patients to resolve problems through seven stages: 1. explanation of the treatment and its rationale 2. clarification and definition of the problems 3. choice of achievable goals 4. generation of alternative solutions 5. selection of a preferred solution 6. clarification of the necessary steps to implement the solution 7. evaluation of progress. Treatment comprised an initial 1-hour session and five followup sessions of 30-45 minutes. Ongoing group supervision of the nurses was carried out by clinical nurse therapists experienced in problem solving.	62% of participants received at least 4 sessions (mean number of sessions completed = 4).	Overall satisfaction score 37.6 (5.8) vs. 31.6 (7.6) in CG. When differences were found between groups with patient satisfaction, these

Appendix F Table 7. Detailed Intervention Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations

Author, Year	IG	Intervention detail	Adherence	Acceptability
				were between the GP and both CMHN treatments, with few differences found between the two nurse groups. Patients in the CMHN groups were significantly more likely to agree that they found the treatment helpful and would recommend it to a friend. Patients in the CMHN groups were significantly more likely to disagree with the statement that they did not receive the best treatment possible. Patients in the CMHN groups were significantly more likely to agree that their problems had been identified and they had help in dealing with them. Patients in both

Appendix F Table 7. Detailed Intervention Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations

Author, Year	IG	Intervention detail	Adherence	Acceptability
				CMHN groups were significantly more likely to agree they had help planning what to do between appointments; however, slightly more in the PST group reported this.
Kendrick, 2005[146]	IG2	Nurses in the generic CMHN treatment arm were asked to help patients become well as quickly as possible using whatever treatments they were experienced in giving, which could include counseling and support. They were asked to offer patients the same number of therapy sessions as the problem-solving CMHNs. The CMHNs in this arm did not receive any supervision over and above the supervision that they usually received in their trust post. Treatment sessions were offered at a place convenient to the patient. This could be their home, GP surgery, or other NHS location, for instance the CMHN base.	Patients attended an average of 4.4 sessions, 73% received 4+ sessions	(See above).
King, 2000[147]	IG1	Cognitive behavior therapy was provided by clinical psychologists who were qualified for accreditation by the British Association for Behavioral and Cognitive Psychotherapies. Treatment was to be provided over an average of 6 sessions per patient, with a maximum of 12 sessions, typically lasting 50 minutes. Sessions were offered, as far as possible, on a weekly basis at the general practice. Longer intervals were used on occasion with the agreement of the patient. Psychologist training: Psychologists were accredited by the British Association for Behavioral and Cognitive Psychotherapies (BABCP) and were eligible for registration with the United Kingdom Council for Psychotherapy. The requirements include core professional training in therapeutic and interpersonal issues, additional training in CBT, and a period of closely supervised clinical practice. Because CBT is a more structured treatment, the therapists were given detailed manuals (for both therapist and patient) that described a problem-formulation and staged-intervention approach. Psychologists in	30% of participants received at least 7 sessions, 51% received 2-6 sessions, 5% received 1 session, and 14 received 0 sessions.	Scoring 1-5, high scores better: at 4 mo: IG1=3.71, IG2=3.93, CG=3.27 (F=12.46, df = 2, p = 0.001 [post hoc Scheffe test, CG <IG1&2]) at 12 mo: IG1=3.75, IG2=3.79, CG=3.40 (F=3.66, df = 2, p = 0.03 [post hoc Scheffe test, CG <IG2]).

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Author, Year	IG	Intervention detail	Adherence	Acceptability
		Salford also received a brief training session from a psychologist employed at Manchester University (Dr. Adrian Wells) to further assist in standardizing their clinical methods.		
King, 2000[147]	IG2	Non-directive counseling was provided by counselors who were qualified for accreditation by the British Association for Counselling. Treatment was to be provided over an average of 6 sessions per patient, with a maximum of 12 sessions. Most sessions were 50 min, but some were scheduled 30-min sessions. Sessions were offered, as far as possible, on a weekly basis at the general practice. Longer intervals were used on occasion with the agreement of the patient. Psychologist training: All the counselors involved in the trial had the necessary qualifications and experience to be accredited by the British Association for Counselling (BAC). The counsellors complied with a non-directive approach, which was outlined in a brief manual provided by the research team. All the counselors received an explanation of the study in full, with special attention paid to the need to avoid providing treatment that could be confused with CBT. Although it was agreed that CBT techniques might be used very occasionally (e.g., if they were required to overcome a therapeutic impasse), it was stressed that the treatment must be predominantly nondirective in nature.	The vast majority of appointments lasted 50 minutes. 10.4% attended 0 sessions, 4.5% attended just 1 session, 37.3% attended 2-6 sessions, 47.8% attended 7 or more.	Scoring 1-5, high scores better: at 4 mo (n=44): 3.93 (F=12.46, df = 2, p = 0.001 [post hoc Scheffe test, GP < NDC and CBT]) at 12 mo (n=36): 3.79 (F=3.66, df = 2, p = 0.03 [post hoc Scheffe test, GP < NDC]). Satisfaction differed significantly between the three groups at 4- and 12-month followups.
Lam, 2010[148]	IG1	Each subject in the PST-PC group returned to the clinic to see a Family Medicine trainee who was not involved in the usual care of the patient for three problem-solving treatment in primary care (PSTPC) sessions at week 1, 3, and 5 from time of screening. The PST-PC was modified from that used by Mynors-Wallis et al. Session one lasted 30-45 min during which the doctor completed the three core tasks of PST-PC: (1) establishment of a positive therapeutic relationship, (2) developing a shared understanding of the problem, and (3) promoting change in behavior, thoughts and emotions. Sessions two and three each lasted for 20-30 min during which the doctor assessed the patient's progress, answered questions, and reinforced the patient's coping behaviors and positive thinking. A semi-structured record form incorporating the seven steps of PST-PC was used to monitor treatment process during each	73% of participants received all 3 sessions; 89% received at least 1 session.	Only a minority of subjects thought the PST-PC improved their general health (33%) or psychological health (39%).

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Author, Year	IG	Intervention detail	Adherence	Acceptability
		session.		
Lang, 2006[149]	IG1	"Play Your Cards Right" (Cards) is a brief psychotherapy for primary care patients, which follows the basic structure of problem-solving therapy. The intervention is composed of four 30- to 60-min one-on-one meetings. The first meeting takes place in person; the remainder may be held by telephone if the patient elects that option. In the first session of Cards, patients are presented with a bell-shaped curve meant to represent the way that they are functioning. The left tail is labeled "Under Performing"; the center, "Optimum Zone"; and the right tail, "Maxed Out." Patients are given three cards (the origin of the title of the intervention) on which the words "People," "Commitments," and "Health" are printed. Patients are asked to place the cards on the figure in order to assess how they are functioning in each area. The goal of the intervention is to move all of the cards to the "Optimum Zone." Patients select a card on which to focus and identify a problem that they believe is contributing to the position of the target card. Next, they are asked to identify possible strategies for addressing the problem and to complete worksheets to evaluate the usefulness of these strategies. If they are able to generate a potentially useful strategy in this way, patients set a goal to implement that strategy in the next week using a worksheet for good goal setting (e.g., make a specific and attainable goal, plan a reward). If they are not able to generate a strategy on their own, they are asked to review a list of possible techniques in a "Client Guide" and to select one to try. The Client Guide also contains an introductory section that explains the problem-solving strategy; patients are asked to review that material before the next session. A "Self Card," a laminated index card that lists each of the steps of the problem-solving process, also is provided to prompt patients to follow these steps on their own. In subsequent sessions, patients begin by evaluating the outcome of the strategy they selected in the previous meeting. Next, they practice the process of positioning cards, reviewing problems, selecting strategies, and setting goals. After the first session, there is more emphasis on helping the patient to learn the supplementary techniques presented in the Client Guide. These techniques are adapted from a number of psychotherapeutic approaches, including cognitive behavioral therapy for depression and anxiety, rational-emotive behavior therapy, interpersonal therapy, acceptance and commitment therapy, and	72% of participants received all 4 sessions.	After the first session, patients (n = 27) generally found Cards to be logical (M = 7.4, SD = 0.8, range = 6–8), were confident it would be helpful (M = 6.6, SD = 1.3, range = 4–9), felt it would help them solve problems (M = 6.3, SD = 1.3, range = 4–8), and would recommend it to a friend (M = 6.7, SD = 1.4, range = 3–8). At the end of the intervention, patients who completed (n = 23) were generally satisfied with the results of the program (on a scale of 1–5, M = 4.3, SD = 0.9, range = 2–5) and would recommend it to a friend (M = 4.5, SD = 0.8, range = 2–5).

Appendix F Table 7. Detailed Intervention Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations

Author, Year	IG	Intervention detail	Adherence	Acceptability
		solution-focused brief therapy. The decision as to whether the next meeting will be in person or by telephone is made by the patient at the end of the preceding session. Of the 28 people who entered treatment, 11 chose to focus on the health card, 10 on the people card, and 7 on the commitments card. The most commonly referenced supplementary techniques presented in Sessions 2-4 were cognitive restructuring (presented to 66% of patients), relaxation skills (64%), and communication skills (60%). All other supplementary skills were presented to 30% or fewer of the patients.		
Linden, 2005[150]	IG1	25 CBT tx sessions were planned, each session 50 min.	Mean number of sessions completed = 22.	NR
Nordgren, 2014[151]	IG1	The ICBT treatment was a form of text-based guided self-help treatment with therapist support via the internet that consisted of 7-10 treatment modules, or chapters, per participant covering a period of 10 weeks. The modules have been shown to be effective previously when used on specific diagnosed samples (i.e., panic disorder), social phobia, generalized anxiety disorder, and depression and were adapted to be able to be presented together in the tailored format by being slightly rewritten (e.g., words relating to specific conditions were removed). Tailoring included both the order of treatment modules, the amount of text presented to the participant and how many modules to include in the 10-week treatment protocol. The same seven MSc students who conducted the SCID interviews served as Internet therapists. The therapists had access to supervision by a licensed clinical psychologist both regarding the format and client-specific questions throughout the study period. All communication between participants and therapists was made through the internet, using a messenger system within the treatment platform similar to e-mail, and the main nature of the feedback was to answer any questions regarding the module and homework assignments. Each module consisted of text and illustrations presenting a specific symptom and exercises and were to be completed by 3-8 essay questions to be worked through during a period of 1 week. Some of the modules (i.e., relaxation and mindfulness) had audio files attached to them for the participants to listen to. The homework questions were intended to encourage learning and to help the Internet therapist assess whether the participants had assimilated the	32% of participants completed all modules (mean number of modules completed = 53%).	NR

Appendix F Table 7. Detailed Intervention Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations

Author, Year	IG	Intervention detail	Adherence	Acceptability
		material or not. Participants were asked to answer the questions and provide worksheets and report on outcomes of different exercises to their therapist once a week. Following submission of the report, they were given individual feedback, most often within 24 hours. When the therapist received a homework assignment showing that the participant has assimilated the material, the next module was made accessible through an encrypted message exchange system. The therapists were instructed not to spend more than 15 min per participant per week in reading and communicating feedback. Prescribed modules were available for download in PDF format, and participants were advised to print out or to download the self-help material to have the material readily available. The first module (introduction) and the last (relapse prevention) were fixed, which gave the possibility to tailor the treatment by adding any of the following: cognitive restructuring (2 modules), social anxiety (2 modules), generalized anxiety (3 modules), panic disorder (2 modules), agoraphobia, behavioral activation (2 modules), applied relaxation, mindfulness, assertiveness, problem solving, stress management, and sleep. All modules, except for cognitive restructuring, applied relaxation, assertiveness, problem solving, and stress management, were disorder specific in that they targeted core symptoms of each of the diagnoses.		
O'Mahen, 2022[152]	IG1	The ACORN intervention comprised a manualized group intervention, delivered as three 90-min group sessions, led by a midwife and psychological provider (e.g., trainee clinical psychologist) who attended a 3-day training in the intervention by HOM. Sessions were audiotaped and reviewed for fidelity at group supervision sessions, led by HOM. Treatment sessions were held at 3-week intervals, with the aim of maintaining participant engagement, balancing participant attendance in group sessions with their medical appointments, whilst also providing participants with time to try out practical strategies in between sessions. The three group sessions covered key themes determined in collaboration with the research literature and our PPI group. Sessions focused on perinatal adapted strategies to managing worry. The primary strategies were centered on problem-solving and managing uncertainty. Managing uncertainty strategies were adapted from Dugas[68] and also included mindfulness-based approaches that were acceptance and compassion-focused (i.e., loving-kindness towards the fetus). Given the importance of	In total, 44/57 (77%) of participants allocated to the intervention program and 26/44 (60%) of partners attended at least one of the three intervention sessions. Consistent with England's IAPT service definition of adherence as two or more sessions, 51%.	NR

Appendix F Table 7. Detailed Intervention Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations

Author, Year	IG	Intervention detail	Adherence	Acceptability
		social support during the perinatal period, sessions also included content on communicating about problem-solving with important others. Participants were asked to schedule soothing, self-care related activities each session. See Table 1 for details about the content of each session. All participants in the intervention arm continued to receive their usual care during pregnancy and had access to the usually available range of interventions for prenatal anxiety and other physical and mental health problems.		
Proudfoot, 2004[153]	IG1	Interactive, multimedia computerized cognitive–behavioral therapy package consisting of a 15-min introductory videotape, followed by eight therapy sessions. Each weekly session lasts about 50 min, with "homework" projects between the sessions. Modules include: Automatic thoughts, Thinking errors and distraction, Challenging unhelpful thinking, Core beliefs, Attributional style, and Action planning.	NR	Average satisfaction in the computerized therapy group was 1.68 (95% CI 0.82–2.54) points higher than in the treatment-as-usual group.
Rollman, 2018[154]	IG1	Intervention involved a computerized CBT program and up to 13 15- to 30-minute phone contacts with a care manager. The computerized cognitive behavioral therapy (CCBT) program (Beating the Blues) consists of a 10-minute introductory video followed by eight 50-minute interactive sessions that our care managers encouraged patients to complete every 1 to 2 weeks. Each session used easily understood text, audiovisual clips, and "homework" assignments to impart basic CBT techniques, and patients completed the GAD-7 and PHQ-9 at the start of each CCBT session to self-track their symptoms. Care managers emailed their assigned patients a web link to the CCBT program and requested a time to schedule an introductory telephone call to review the program and establish rapport. Later, they logged into the CCBT program's clinical helper portal to monitor their patients' progress (e.g., sessions completed, self-reported symptoms, and problems they chose to address), sent personalized feedback and encouragement via email, and contacted patients via telephone who either had not improved or failed to log in regularly. Depending on a patient's symptoms and level of engagement, the care manager emailed or telephoned biweekly for approximately 2 months, and these contacts lasted approximately 15 to 30 minutes. Afterwards, the	37% of participant received all 8 sessions; 84% received at least 1 session (mean number of sessions completed =5).	NR

Appendix F Table 7. Detailed Intervention Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations

Author, Year	IG	Intervention detail	Adherence	Acceptability
		patient transitioned to the continuation phase of care, during which the care manager contacted the patient approximately monthly until the end of our 6-month intervention.		
Rollman, 2018[154]	IG2	Intervention involved an internet support group (ISG), computerized CBT program, and up to 13 15- to 30-minute phone contacts with a care manager. The ISG included discussion boards created by the care manager moderator and study patients, the ISG curated links to external resources, including local $4 generic pharmacy programs, "find-a-therapist" and various crisis hotlines, and brief YouTube videos on insomnia, nutrition, exercise, and other topics, and embedded links to its EMR's patient portal to integrate its use into routine care. To enhance patient engagement, the ISG featured (1) status indicators on members' profiles and comments (e.g., stars and "likes"), (2) email notifications of new ISG activities, (3) automated highlighting of recent comments on members' home pages personalized to their ISG profile and past activities, (4) invited member-guest moderators, and (5) various contests to encourage logins and comments. The computerized cognitive behavioral therapy (CCBT) program (Beating the Blues) consists of a 10-minute introductory video followed by eight 50-minute interactive sessions that care managers encouraged patients to complete every 1 to 2 weeks. Each session used easily understood text, audiovisual clips, and "homework" assignments to impart basic CBT techniques, and patients completed the GAD-7 and PHQ-9 at the start of each CCBT session to self-track their symptoms. Care managers emailed their assigned patients a web link to the CCBT program and, if applicable, the ISG and requested a time to schedule an introductory telephone call to review the program(s) and establish rapport. Later, they logged into the CCBT program's clinical helper portal to monitor their patients' progress (e.g., sessions completed, self-reported symptoms, and problems they chose to address), sent personalized feedback and encouragement via email, and contacted patients via telephone who either had not improved or failed to log in regularly. Depending on a patient's symptoms and level of engagement, the care manager emailed or telephoned biweekly for approximately 2 months, and these contacts lasted approximately 15 to 30 minutes. Afterwards, the patient transitioned to the continuation phase of care, during which the care manager contacted the patient approximately	Overall, 228 of 302 patients (75.5%) in the CCBT+ISG arm logged into the ISG at least once, of whom 141 (61.8%) made at least 1 online comment or post (mean, 10.5; median, 3; range, 1-306).	NR

Appendix F Table 7. Detailed Intervention Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations

Author, Year	IG	Intervention detail	Adherence	Acceptability
		monthly until the end of the 6-month intervention.		
Schreuders, 2007[156]	IG1	The treatment is brief (less than 4 hours) and focuses on practical skill building. It consists of a maximum of six sessions, each of which contains seven steps of problem solving: (1) Explanation and rationale, (2) problem definition, (3) establishing achievable goals, (4) generating solutions, (5) selecting preferred solution, (6) implementing solution, (7) evaluation of progress. Steps are applied in a systematic manner to achieve problem resolutions for everyday problems, such as not being able to do all the housework in one day, or not being able to do activities they like. Four to six sessions, first session maximum of 60 min, next sessions maximum of 30 min.	NR	NR
Seekles, 2011[157]	IG1	Stepped care: The stepped care program consists of four evidence-based interventions: (1) Watchful waiting for 4 weeks, (2) 5-week guided Problem Solving Treatment self-help program, (3) a phobia-specific self-help intervention for those with phobias, and (4) Medication and/or specialized mental health care, which occurred after the final assessment reported in Seekles 2011. The patients were monitored after each step and depending on the outcome, the care manager decided whether or not the patient should "step-up." GPs were asked to refrain from offering any treatment to patients who were included in the stepped care group (treatment group). Benzodiazepines were allowed in both study groups. Patients in the stepped care group were only allowed to receive antidepressants in later phase of the treatment protocol. All patients start with the same tx; however, patients with more severe disorders were referred to specialized MH care for face-to-face psychotherapy and/or pharmacotherapy directly (skipping the self-help intervention and the PST). The severity of the disorders was based on questions about daily functioning on the Work and Social Adjustment Scale (WSAS); when the patient experienced extreme dysfunctioning (a score of 8 or higher) on at least three of the four domains (household tasks, work, social relations and social activities) he or she was directed to specialized mental health care. Patients received no treatment for 4 weeks (watchful waiting). After 4 weeks, the patients in the stepped care program commenced (guided) self-help, starting with one 30-minute face-to-face session with a psychiatric nurse. This session enabled the psychiatric nurse to check for exclusion criteria (e.g., severe psychopathology), to give psychoeducation (e.g., advice on lifestyle) and	62% of participants received the problem-solving therapy intervention; 16% received the phobia intervention. Mean number of lessons completed online = 1 (out of 6 lessons). 15% were referred for medication and/or specialized mental health care after the last study assessment. None of the participants contacted the coach for feedback.	Of those patients who received PST, about half preferred the book (n= 18) while the other half (n= 16) preferred the Internet version.

Appendix F Table 7. Detailed Intervention Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations

Author, Year	IG	Intervention detail	Adherence	Acceptability
		to explain the self-help interventions. Self-help interventions: (1) Generic intervention based on Problem Solving Treatment via book or internet; takes 5 weeks to complete: Offered a 6-step procedure which assists them in solving their worries and problems; participants could choose to follow this course via the internet or by using a book and they could opt to receive feedback on assignments. If they applied for feedback, they were supported by email (the Internet group) or by telephone (the book group). The feedback was given by junior psychologists and was not therapeutic in nature. (2) The second self-help intervention is aimed specifically at patients with phobias and is based on exposure therapy. Participants first have to make a list of all the situations that provoke anxiety and rank these in order of intensity. Next, they make a plan to practice exposure to these situations based on this anxiety hierarchy. This course takes 6 weeks to complete and is only available as a book. Feedback is therefore provided by telephone. During the first session, the psychiatric nurse decides together with the patient, and based on the symptoms, which self-help course is most suitable.		
Stanley, 2009[158]	IG1	Five experienced therapists provided CBT in up to 10 individual sessions over 12 weeks. Cognitive behavior therapy included education and awareness, motivational interviewing, relaxation training, cognitive therapy, exposure, problem-solving skills training, and behavioral sleep management. Brief telephone booster sessions were offered at 4, 7, 10, and 13 months.	Mean number of sessions completed = 7. Mean ratings of adherence = 8; mean ratings of competence = 7 (on a 0-8 scale with higher scores signifying greater adherence/competence).	NR
Stanley, 2014[159]	IG1	CBT occurred over 6 months. During the first 3 months, patients received up to 10 skill-based sessions, including core (education, awareness training, and motivational interviewing; deep breathing; coping self-statements) and elective skills (behavioral activation, exposure, sleep management, problem solving, progressive muscle relaxation, thought stopping and cognitive restructuring) skills. Providers recommended skill modules based on an algorithm. However, in an effort to mirror real-world care and person-centered approaches where patients make choices about which treatment recommendations to follow, after discussion of recommended skills, patient preference determined which modules to	Mean number of sessions completed = 8. Mean ratings of adherence = 8; mean ratings of competence = 7 (on a 0-8 scale with higher scores signifying greater adherence/competence).	NR

Appendix F Table 7. Detailed Intervention Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations

Author, Year	IG	Intervention detail	Adherence	Acceptability
		include. Sessions 1 and 2 were in person. Subsequent sessions occurred either in person or by telephone, depending on patient preference. Workbook pages with information summaries and practice exercises were provided during in-person sessions or via mail before telephone meetings. Clinicians contacted patients to review skills and answer questions 2–3 days after each skill-training session. During the second 3 months, patients were called weekly for 4 weeks and then biweekly for 8 weeks to review skills and provide support for continued practice and skills use.		
Suchan, 2022[160]	IG1	The Wellbeing Course for New Moms is a transdiagnostic course based on the principles of CBT. It was adapted from the Wellbeing Course to reflect the common concerns faced by new mothers. Clients accessed the course through the Online Therapy Unit web platform. Clients completed 5 web-based lessons spanning over the course of 8 weeks, with weekly support from a therapist. Online lessons: The lessons resemble a Microsoft PowerPoint presentation, which participants can read through independently and move through at their own pace. Lesson 1 (1 week) provides psychoeducation about anxiety and depression in general and in postpartum populations; description of symptoms; and explanation of the relationship between unhelpful thoughts, physical symptoms, and unhelpful behaviors. Lesson 2 (2 weeks) provides information on unhelpful thoughts in relation to the CBT model and strategies for monitoring and challenging thoughts. Lesson 3 (1 week) comprises psychoeducation on physical symptoms in relation to the CBT model and strategies for managing both under- and overarousal (e.g., controlled breathing). Lesson 4 (2 weeks) focuses on information related to unhelpful behaviors in relation to the CBT model and guidelines about behavioral activation and graded exposure. The fifth and final lesson (2 weeks) includes information about relapse prevention, normalization, and creation of relapse prevention plans. Each lesson includes case stories and do-it-yourself guides that were modified to be relevant to new mothers to promote the practice of strategies from the course, as well as additional resources that could be accessed at any point throughout the course (i.e., assertiveness, managing beliefs, communication, mental skills, managing panic attacks, managing posttraumatic stress disorder, sleep hygiene, problem-solving and worry time, and balancing new motherhood). A new resource (i.e., balancing new motherhood) was created for the purpose of this study to	75% (21/28) of the participants completed at least four of the five lessons, and 50% (14/28) of the participants completed all 5 lessons. Number of log-ins, mean: 22.25 Messages sent to the therapist, mean: 5.32 Messages received from therapist, mean: 9.8	Tx satisfaction: Would recommend the course to a friend: 100%. The course was worth their time: 100%. Satisfied or very satisfied with the treatment: 95% Satisfied or very satisfied with course materials 91% Increased or greatly increased confidence in managing symptoms: 95% Increased or greatly increased motivation to seek additional treatment if needed in the future: 77%

Appendix F Table 7. Detailed Intervention Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations

Author, Year	IG	Intervention detail	Adherence	Acceptability
		specifically provide information about PPD and PPA, as well as common struggles that new mothers face (e.g., limited sleep, new roles, isolation, and low self-esteem). Therapist support: All clients assigned to ICBT received weekly therapist support from a master-level, registered social worker trained in the provision of ICBT. The therapist contacted clients on the same day each week throughout the 8-week course using secure emails on the Online Therapy Unit's platform. In this way, communication between the client and therapist was asynchronous, meaning that the sender's message may not be read until several days later by the receiver. Each therapist message was personalized but included several important elements: warmth and concern, feedback on symptom measures, highlighting key skills, answering client questions about the lessons, acknowledging any stated areas of difficulty, providing encouragement reinforcing progress, managing risk, and reminding clients about course instructions. Phone calls were made to clients in specific cases (i.e., heightened risk of suicide, significant increase in symptoms of anxiety or depression, or to clarify client concerns). The clients also received automated messages as reminders of new lessons or questionnaires to complete. Clients received an average of 9.89 (SD, 1.03) messages and 1.93 (SD, 1.96) phone calls from their therapists and sent an average of 4.32 (SD, 5.23) messages.		
Sundquist, 2015[161]	IG1	The mindfulness-based group therapy (MGT) lasted 8 weeks and was given in 2-hour sessions, once a week. Sessions included structured and controlled meditative exercises. The participants were also instructed to practice mindfulness at home for 20 min/day and were given a compact disc, a training manual, and a diary for this purpose. On average, the participants undertook 102 individual-based mindfulness sessions (sd = 44, range 0–219). Two mindfulness instructors were present at each group session and each group consisted of a maximum of 10 participants. Participants were asked to wear comfortable clothes and to bring a mat or blanket for some of the exercises. All participants received pharmacological treatment, if deemed necessary, and followup by the doctor at the general practice.	62% received 6-8 sessions; 11% of participants received 1-5 sessions.	NR
Torres-Platas, 2019[162]	IG1	Weekly 2-hour group sessions for 8 weeks, based on the MBCT manualized protocol. Participants were encouraged to try different mindfulness techniques during sessions (e.g., silent meditation, body	NR	23 participants in intervention arm reported positive

Appendix F Table 7. Detailed Intervention Characteristics for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations

Author, Year	IG	Intervention detail	Adherence	Acceptability
		scans, 3-minute breathing space, gentle arm movements, chair yoga postures, guided meditations, and compassion meditations). Group discussions focused on reinforcing the guiding principles of mindfulness: awareness, non-judgment, and acceptance. At the end of each weekly session, participants received a sheet with specific instructions on how to complete daily home mindfulness practices, learned during the MBCT group. Home practice consisted of roughly at least 15 minutes of seated meditation and 10 minutes of informal mindfulness (e.g., mindful: walking, brushing their teeth, eating) daily. In addition, participants received electronic reminders about their homework and a summary of home practice, with meditation CDs/online versions as support material.		effects about the intervention and the interventionists.
Vera, 2021[163]	IG1	CBT for GAD consisted of 15 individual sessions of 1.5 hours. Sessions were delivered weekly, except for a separation of 2 weeks before the final session. The intervention followed a manualized CBT intervention for GAD. The manual was translated to Spanish and culturally adapted to include language, idioms, and examples relevant to Latino culture. Special emphasis was placed on the attainment of conceptual and cultural equivalence, while maintaining fidelity to the active core elements in the English CBT manual. The intervention is based on four main components: self-monitoring, applied relaxation training, cognitive therapy, and the rehearsal of learned coping responses. Participants were encouraged to use applied relaxation techniques learned during treatment to cope with anxiety and worry. Targeted muscle relaxation exercises aimed to increase participants' ability to rapidly produce relaxation to interrupt emerging anxiety and worry spirals. The accuracy of cognitions was examined through the evaluation of their logic, probability, and past evidence, using strategies such as, decatastrophizing, worry outcome diary, and the Socratic method. The practice and implementation of newly learned relaxation and cognitive coping responses was emphasized throughout treatment to facilitate replacing habitual perspectives of worrisome activity with more adaptive ones.	Tx completed (15 sessions or more) by 42.3% in the CBT group. The average number of sessions attended was 9 for CBT.	NR

Abbreviations: CBT = cognitive behavioral therapy; CCBT = computerized cognitive behavioral therapy; CG = control group; CMHN = community mental health nurse; GAD = Generalized Anxiety Disorder assessment; GP = general practitioner; ICBT = Internet-delivered cognitive behavior therapy; IG = intervention group; MBCT = mindfulness-based cognitive therapy; NDC = non-directive counseling; NHS = National Health Service; PHQ = Patient Health Questionnaire; PST-PC = problem solving therapy – primary care; PTSD = post-traumatic stress disorder; SCID = Structured Clinical Interview for DSM-5; SD = standard deviation.

Appendix F Table 8. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Anxiety (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Cuijpers, 2016[164]	RCTs in adults with MDD, GAD, PAD, or SAD. Only trials in which recruited subjects met diagnostic criteria for the disorder according to a structured diagnostic interview, such as the Structured Clinical Interview for DSM (SCID), the Composite International Diagnostic Interview (CIDI), or the Mini International Neuropsychiatric Interview (MINI); comorbid mental or somatic disorders were not used as an exclusion criterion.	Any therapy in which cognitive restructuring was one of the core components; also included purely behavioral therapies (i.e., trials of behavioral activation for depression and exposure for anxiety disorders); therapies that used individual, group, and guided self-help formats, but excluded self-guided therapies without any professional support, because their effects have been found to be considerably smaller than other formats.	Only studies using waiting list, care-as-usual, or pill placebo control groups. Care-as-usual was defined broadly as anything patients would normally receive, as long as it was not a structured type of psychotherapy.	NR	Used all measures examining depressive symptoms, such as the Beck Depression Inventory (BDI-28 or BDI-II-29) and the Hamilton Rating Scale for Depression, or anxiety symptoms, such as the Beck Anxiety Inventory, the Penn State Worry Questionnaire, the Fear Questionnaire, and the Liebowitz Social Anxiety Scale.
Cuijpers, 2016[9]	Adults with PD (with or without agoraphobia), generalized anxiety disorder (GAD), social anxiety disorder (SAD), or major depressive disorder (MDD).	RCTs with a cognitive or behavioral treatment.	Compared to a control group (waiting list, care as usual, placebo or other).	NR	Focused only on depressive symptoms as measured with BDI, the BDI-II, and HAMD-17.
Gould, 2012[165]	Participants were age 55 years and older (studies examining older and younger people were included if age-specific analyses were reported); participants had a diagnosis of PD, GAD, agoraphobia, phobia,	One of the treatment arms comprised CBT that lasted longer than two sessions.	Active control (defined as other treatment, such as pharmacotherapy, or a social support or attention placebo, such as supportive psychotherapy or counseling, psychoeducation, discussion group, or	Community outpatient clinics	Evidence-based anxiety outcome measures were used to assess the effectiveness of CBT. Depression outcome measures were also included given the prevalence of comorbid anxiety and mood

Appendix F Table 8. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Anxiety (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
	PTSD, OCD, or anxiety disorder not otherwise specified (ADNOS); the number of participants in each condition was five or more at any time.		enhanced treatment as usual involving support every week or every other week) or a nonactive control (defined as no social support or attention placebo or other treatment, e.g., minimal contact treatment-as-usual or waiting list).		disorders.
Hofmann, 2014[166]	Studies included a sample diagnosed with one or more anxiety disorders; they included a sample of adults age ≥18 years.	Studies included at least one cognitive behavioral intervention, and if this was the primary treatment (i.e., not an adjunct to a primarily pharmacological intervention); they included at least one measure of QOL at pre- and post-intervention.	NR	NR	At least one measure of QOL at pre- and post-intervention.
Li, 2022[84]	Women who 1) were pregnant or postpartum (i.e., within 12 months post-delivery) and 2) had risk factors for perinatal depression, anxiety and/or stress at baseline.	Only trials of interventions explicitly stating the use of CBT alone or CBT with a co-intervention (CBT-CI).	Control groups include no-intervention control, treatment as usual (TAU), enhanced TAU, waitlist, attention controls (e.g., standard parenting education), informational booklet about TAU, or active controls.	No restrictions	Short-term efficacy was defined as mean score changes in depression, or anxiety symptoms from baseline (i.e., pre-intervention assessment) to immediately post-intervention. Long-term efficacy was defined as mean score changes from baseline to the end of followup (~12 months).

Appendix F Table 8. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Anxiety (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Ponting, 2020[89]	Study participants had to be a) pregnant women, b) 18 years or older, and c) residing in the United States. Further, a majority of the sample (75% or more) had to identify as Latina/Hispanic or Black/African American.	Psychological interventions were inclusive of manualized psychoeducational strategies, cognitive behavioral therapy, interpersonal psychotherapy, psychodynamic therapy, acceptance and commitment therapy, and mindfulness training delivered during the prenatal period via telephone, home, or clinic visits, or individual or group sessions by a health professional or lay person.	NR	NR	Studies also had to measure depression and anxiety symptoms as an outcome using standardized depression and anxiety instruments (e.g., EPDS).
van Dis, 2020[167]	Studies were included if they tested adult patients (or samples consisting mostly of adults but also some adolescents age ≥16 years) who received a diagnosis of GAD, PD, SAD, specific phobia, PTSD, or OCD based on results of a structured diagnostic interview.	RCTs that examined effects of CBT (i.e., any therapy with cognitive restructuring and/or a behavioral therapy, such as exposure, as core component), including third-generation CBTs (i.e., acceptance and commitment therapy and metacognitive therapy), at least 1 month after treatment completion, in an individual, group, or internet treatment format.	Comparison groups included care as usual (i.e., anything patients would normally receive as long as it was not a structured type of psychotherapy, such as primary care at medical centers or case management with educational groups), relaxation, psychoeducation, pill placebo, supportive therapy, or waiting list.	Excluded studies if they tested inpatients.	NR

Appendix F Table 8. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Psychological Treatment of Anxiety (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Weaver, 2017[93]	Adults older than age 18 years; rural or remote population.	(a) The sample or intervention delivery site was identified as rural or remote; (b) the intervention was a CBT-based program and included at least one core treatment element (e.g., behavioral activation, cognitive restructuring, exposure); (c) the primary aim of the intervention study was to reduce the symptoms or incidence of depression and/or anxiety disorders, and the primary outcome measure was symptoms or diagnosis of the targeted disorder; (d) study participants were adults; and (e) the study was published in a peer-reviewed, English-language journal.	No requirement.	NR	Clinical diagnosis, symptom measures, or clinical judgment.

Abbreviations: BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; EPDS = Edinburgh Postnatal Depression Scale; GAD = generalized anxiety disorder; HAM-D = Hamilton Rating Scale for Depression; MDD = major depressive disorder; NR = not reported; OCD = obsessive compulsive disorder; PAD = panic disorder; PTSD = post-traumatic stress disorder; QOL = quality of life; RCT = randomized controlled trial; SAD = social anxiety disorder.

Appendix F Table 9. Anxiety Symptom Severity Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Corpas, 2021 (G)(A or D)[142]	GAD-7	0-21	Worse	All	IG1	8	53	52	10.9 (4.6)	11.6 (4.1)	-3.7 (4.4)	-1.4 (4)	-2.3 (-3.9 to -0.7)	0.007	NR
Corpas, 2021 (G)(A or D)[142]	PHQ-PD	0-15	Worse	All	IG1	8	53	52	7.8 (4.7)	7.9 (4.5)	-4.1 (4.1)	-0.2 (4.7)	-3.9 (-5.5 to -2.2)	<0.001	NR
Gensichen, 2019[144] (G)(A)	BAI	0-63	Worse	All	IG1	26	230	189	28.3 (14.7)	28.2 (13.3)	-8.5 (13.2)	-5.3 (13.9)	-3 (-5.8 to -0.2)	0.033	No
Gensichen, 2019[144] (G)(A)	BAI	0-63	Worse	All	IG1	52	230	189	28.3 (14.7)	28.2 (13.3)	-10.2 (14.5)	-6.1 (14.1)	-4 (-6.9 to -1.2)	0.006	No
Nordgren, 2014[151] (G)(A)	BAI	0-63	Worse	All	IG1	10	50	50	21.2 (9.7)	21.3 (9.7)	-9.4 (8.9)	-5 (8.9)	-4.3 (-7.8 to -0.9)	<0.05	NR
Proudfoot, 2004[153] (G)(A or D)	BAI	0-63	Worse	All	IG1	8	99	98	18.3 (10.2)	19.4 (9.3)	-7.4 (9.4)	-5 (9.7)	-2.4 (-5.1 to 0.3)	0.17	Yes
Proudfoot, 2004[153] (G)(A or D)	BAI	0-63	Worse	All	IG1	13	93	85	18.3 (10.2)	19.4 (9.3)	-8 (9.5)	-7 (9.7)	-1 (-3.8 to 1.8)	0.17	Yes
Proudfoot, 2004[153] (G)(A or D)	BAI	0-63	Worse	All	IG1	21	84	80	18.3 (10.2)	19.4 (9.3)	-8.7 (9.7)	-9 (8.7)	0.3 (-2.5 to 3.1)	0.17	Yes
Proudfoot, 2004[153] (G)(A or D)	BAI	0-63	Worse	All	IG1	34	91	91	18.3 (10.2)	19.4 (9.3)	-9.4 (9.4)	-8.5 (9.2)	-0.9 (-3.6 to 1.8)	0.17	Yes
Roy-Byrne, 2010[155] (G)(A)	BSI-12	NR	Worse	All	IG1	26	503	501	16.4 (9.8)	16.2 (9)	-7.2 (8.5)	-4.6 (8.9)	-2.6 (-3.7 to -1.6)	<0.001	No
Roy-Byrne, 2010[155] (G)(A)	BSI-12	NR	Worse	All	IG1	52	503	501	16.4 (9.8)	16.2 (9)	-8.2 (8.6)	-5.4 (8.9)	-2.8 (-3.9 to -1.7)	<0.001	No

Appendix F Table 9. Anxiety Symptom Severity Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Roy-Byrne, 2010[155] (G)(A)	BSI-12	NR	Worse	All	IG1	78	503	501	16.4 (9.8)	16.2 (9)	-8.2 (9.6)	-6.4 (9)	-1.8 (-2.9 to -0.6)	0.05	No
Roy-Byrne, 2010[155] (G)(A)	BSI-12	NR	Worse	GAD	IG1	26	390	366	16.2 (NR)	16.3 (NR)	-7 (NR)	-4.6 (NR)	-2.5 (-3.8 to -1.3)	0.002	No
Roy-Byrne, 2010[155] (G)(A)	BSI-12	NR	Worse	GAD	IG1	52	390	366	16.2 (NR)	16.3 (NR)	-8.1 (NR)	-5.5 (NR)	-2.7 (-3.9 to -1.5)	<0.001	No
Roy-Byrne, 2010[155] (G)(A)	BSI-12	NR	Worse	GAD	IG1	78	390	366	16.2 (NR)	16.3 (NR)	-8 (NR)	-6.4 (NR)	-1.7 (-2.9 to -0.5)	0.05	No
Roy-Byrne, 2010[155] (G)(A)	BSI-12	NR	Worse	PD	IG1	26	235	240	19.2 (NR)	19 (NR)	-8.5 (NR)	-5.6 (NR)	-2.7 (-4.4 to -1)	0.02	No
Roy-Byrne, 2010[155] (G)(A)	BSI-12	NR	Worse	PD	IG1	52	235	240	19.2 (NR)	19 (NR)	-10.2 (NR)	-6.9 (NR)	-3.2 (-4.9 to -1.4)	0.004	No
Roy-Byrne, 2010[155] (G)(A)	BSI-12	NR	Worse	PD	IG1	78	235	240	19.2 (NR)	19 (NR)	-10.1 (NR)	-8.3 (NR)	-1.7 (-3.5 to 0.1)	0.35	No
Roy-Byrne, 2010[155] (G)(A)	BSI-12	NR	Worse	SAnD	IG1	26	210	195	16.8 (NR)	17.1 (NR)	-6.6 (NR)	-4 (NR)	-3 (-4.9 to 1.1)	0.02	No
Roy-Byrne, 2010[155] (G)(A)	BSI-12	NR	Worse	SAnD	IG1	52	210	195	16.8 (NR)	17.1 (NR)	-8.1 (NR)	-5.1 (NR)	-3.3 (-5.2 to -1.5)	0.005	No
Roy-Byrne, 2010[155] (G)(A)	BSI-12	NR	Worse	SAnD	IG1	78	210	195	16.8 (NR)	17.1 (NR)	-8.3 (NR)	-6.3 (NR)	-2.3 (-4.2 to -0.6)	0.09	No
Lang, 2006[149] (G)(A or D)	BSI-A	0-72	Worse	All	IG1	4	25	27	66 (9.2)	65.7 (8.8)	-8.3 (10.3)	-2.2 (10.1)	-6.1 (-11.7 to -0.5)	NR	NR

Appendix F Table 9. Anxiety Symptom Severity Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Lang, 2006[149] (G)(A or D)	BSI-A	0-72	Worse	All	IG1	16	22	25	66 (9.2)	65.7 (8.8)	-7.6 (9.5)	-2.3 (9.3)	-5.3 (-10.7 to 0.1)	NR	NR
Lang, 2006[149] (G)(A or D)	BSI-A	0-72	Worse	All	IG1	30	21	25	66 (9.2)	65.7 (8.8)	-5.4 (10.1)	-1.5 (8.7)	-3.9 (-9.3 to 1.5)	0.021	NR
Clark, 2022[141] (G)(A)	GAD-7	0-21	Worse	All	IG1	13	34	33	8.4 (5.4)	9.5 (5.2)	-5.3 (4.7)	-0.4 (5.5)	5.4 (3.6 to 7.1)	<0.001	Yes
Clark, 2022[141] (G)(A)	GAD-7	0-21	Worse	All	IG1	52	34	34	8.4 (5.4)	9.5 (5.2)	-6.3 (4.7)	0 (5.2)	6.8 (5.1 to 8.5)	<0.001	Yes
Clark, 2022[141] (G)(A)	GAD-7	0-21	Worse	All	IG2	13	34	33	9.8 (5.3)	9.5 (5.2)	-4.4 (4.7)	-0.4 (5.5)	3.8 (2.1 to 5.6)	<0.001	Yes
Clark, 2022[141] (G)(A)	GAD-7	0-21	Worse	All	IG2	52	34	34	9.8 (5.3)	9.5 (5.2)	-6.1 (4.6)	0 (5.2)	5.9 (4.2 to 7.6)	<0.001	Yes
Corpas, 2021[142] (G)(A or D)	GAD-7	0-21	Worse	All	IG1	8	53	52	10.9 (4.6)	11.6 (4.1)	-3.7 (4.4)	-1.4 (4)	-2.3 (-3.9 to -0.7)	0.007	NR
Graham, 2020[145] (G)(A or D)	GAD-7	0-21	Worse	All	IG1	4	74	72	11.6 (39.6)	11.2 (39.9)	-3.2 (39.6)	-0.5 (42.2)	2.5 (1 to 4)	NR	No
Graham, 2020[145] (G)(A or D)	GAD-7	0-21	Worse	All	IG1	8	74	72	11.6 (39.6)	11.2 (39.9)	-4.8 (41.9)	-1.4 (43.7)	3.3 (1.8 to 4.8)	NR	No
O'Mahen, 2022[152] (Pr)(A)	GAD-7	0-21	Worse	All	IG1	10	57	57	10.3 (4.4)	9.5 (4.5)	-3.9 (4.1)	-1.9 (4.6)	-1.9 (-3.5 to -0.3)	p<0.1	NR
O'Mahen, 2022 (Pr)(A)	GAD-7	0-21	Worse	All	IG1	18	57	57	10.3 (4.4)	9.5 (4.5)	-4.3 (4.4)	-2.9 (5)	-1.4 (-3.1 to 0.3)	NR	NR

Appendix F Table 9. Anxiety Symptom Severity Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
O'Mahen, 2022 (Pr)(A)	GAD-7	0-21	Worse	All	IG1	34 (34)	57	57	10.3 (4.4)	9.5 (4.5)	-5.1 (4.3)	-3.8 (4.7)	-1.3 (-2.9 to 0.4)	NR	NR
Suchan, 2022[160] (PP)(A or D)	GAD-7	0-21	Worse	All	IG1	8	25	29	13.4 (5)	11.7 (5.5)	-6.8 (4.8)	-2.1 (5.2)	-4.7 (-7.4 to -2.1)	NR	NR
Suchan, 2022 (PP)(A or D)	GAD-7	0-21	Worse	All	IG1	13 (NR)	24	30	13.4 (5)	11.7 (5.5)	-7.6 (4.6)	-3.4 (5.4)	-4.1 (-6.8 to -1.4)	NR	NR
Torres-Platas, 2019[162] (O)(A or D)	GAD-7	0-21	Worse	All	IG1	8	27	26	11.4 (3.8)	12.6 (5.1)	-6.4 (5)	-2 (3.8)	-4.4 (-6.8 to -2)	0.001	No
Roy-Byrne, 2010[155] (G)(A)	GADSS	0-24	Worse	GAD	IG1	26	NR	NR	13.4 (NR)	13.7 (NR)	-4.5 (NR)	-3.3 (NR)	-1.6 (-2.4 to -0.8)	<0.001	Yes
Roy-Byrne, 2010[155] (G)(A)	GADSS	0-24	Worse	GAD	IG1	52	NR	NR	13.4 (NR)	13.7 (NR)	-5.7 (NR)	-3.7 (NR)	-2.3 (-3.2 to -1.5)	<0.001	Yes
Roy-Byrne, 2010[155] (G)(A)	GADSS	0-24	Worse	GAD	IG1	78	NR	NR	13.4 (NR)	13.7 (NR)	-6.1 (NR)	-4.1 (NR)	-2.4 (-3.2 to -1.5)	<0.001	Yes
Stanley, 2009[158] (O)(A)	GADSS	0-24	Worse	All	IG1	13	65	50	11.4 (3.6)	11.3 (3.4)	-2.8 (3.6)	-1.4 (4.1)	-1.4 (-2.8 to 0)	0.19	Yes
Stanley, 2009 (O)(A)[158]	GADSS	0-24	Worse	All	IG1	26	53	42	11.4 (3.6)	11.3 (3.4)	-2.8 (3.8)	-1.6 (4.2)	-1.2 (-2.8 to 0.4)	0.97	Yes
Stanley, 2009[158] (O)(A)	GADSS	0-24	Worse	All	IG1	39	54	42	11.4 (3.6)	11.3 (3.4)	-2.8 (4)	-1.7 (4.5)	-1.1 (-2.8 to 0.6)	0.97	Yes
Stanley, 2009[158] (O)(A)	GADSS	0-24	Worse	All	IG1	52	51	41	11.4 (3.6)	11.3 (3.4)	-2.9 (3.7)	-2.1 (4.2)	-0.8 (-2.4 to 0.8)	0.97	Yes

Appendix F Table 9. Anxiety Symptom Severity Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Stanley, 2009[158] (O)(A)	GADSS	0-24	Worse	All	IG1	61	52	42	11.4 (3.6)	11.3 (3.4)	-2.7 (4.3)	-1.8 (4.1)	-0.9 (-2.6 to 0.8)	0.97	Yes
Stanley, 2014[159] (O)(A)	GADSS	0-24	Worse	All	IG1	26	60	68	11.7 (3.9)	11.9 (4.4)	-2.9 (4)	-0.7 (4.5)	-2.2 (-3.7 to -0.7)	0.003	Yes
Fletcher, 2005[143] (G)(A or D)	HADS-A	0-21	Worse	All	IG1	12	15	15	9.9 (2.2)	10.3 (2.2)	-1.8 (2.8)	-1.8 (2.9)	0.1 (-2 to 2.1)	0.779	NR
Kendrick, 2005[146] (G)(A or D)	HADS-A	0-21	Worse	All	IG1	8	90	78	NR	NR	FU=9.6 (4.2)	FU=9.2 (4)	0.1 (-1.3 to 1.4)	0.925	Yes
Kendrick, 2005[146] (G)(A or D)	HADS-A	0-21	Worse	All	IG1	26	90	78	NR	NR	FU=8.7 (4.5)	FU=7.6 (4.3)	1.6 (0 to 3.2)	0.053	Yes
Kendrick, 2005[146] (G)(A or D)	HADS-A	0-21	Worse	All	IG2	8	79	78	NR	NR	FU=9.8 (3.7)	FU=9.2 (4)	0.7 (-0.8 to 2.1)	0.351	Yes
Kendrick, 2005[146] (G)(A or D)	HADS-A	0-21	Worse	All	IG2	26	79	78	NR	NR	FU=8.2 (3.8)	FU=7.6 (4.3)	0.9 (-0.7 to 2.6)	0.269	Yes
Lam, 2010[148] (O)(A or D)	HADS-A	0-21	Worse	All	IG1	6	149	150	5 (3.7)	4.7 (2.8)	-1 (3.4)	-1.4 (2.9)	0.4 (-0.1 to 1)	0.146	Yes
Lam, 2010[148] (O)(A or D)	HADS-A	0-21	Worse	All	IG1	12	149	150	5 (3.7)	4.7 (2.8)	-1.1 (3.8)	-1.5 (3)	0.4 (-0.1 to 1)	0.146	Yes
Lam, 2010[148] (O)(A or D)	HADS-A	0-21	Worse	All	IG1	26	149	150	5 (3.7)	4.7 (2.8)	-1.3 (3.8)	-1.7 (3)	0.4 (-0.1 to 1)	0.146	Yes
Lam, 2010[148] (O)(A or D)	HADS-A	0-21	Worse	All	IG1	52	149	150	5 (3.7)	4.7 (2.8)	-1.2 (4.1)	-1.6 (3.2)	0.4 (-0.1 to 1)	0.146	Yes

Appendix F Table 9. Anxiety Symptom Severity Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Schreuders, 2007[156] (G)(A or D)	HADS-A	0-21	Worse	All	IG1	13	61	69	8.2 (3.9)	9 (4.1)	-1.5 (3.7)	-1.4 (3.4)	0 (-1.3 to 1.2)	0.558	Yes
Seekles, 2011[157] (G)(A or D)	HADS-A	0-21	Worse	All	IG1	8	55	53	9.7 (4.1)	9.8 (4)	-1 (2.7)	-0.5 (2.9)	-0.5 (-1.5 to 0.5)	0.31	No
Sundquist, 2015[161] (G)(A or D)	HADS-A	0-21	Worse	All	IG1	8	83	86	12 (3.7)	13 (3.2)	NR	NR	0.2 (-0.9 to 1.4)	0.69	No
Linden, 2005[150] (G)(A)	HAM-A	0-56	Worse	All	IG1	14.5	31	32	26.8 (8.3)	24 (8.3)	-9.5 (9.6)	-1.5 (8.6)	-8 (-12.5 to -3.5)	NR	NR
Roy-Byrne, 2010[155] (G)(A)	PDSS-SR	0-28	Worse	PD	IG1	26	NR	NR	13.8 (NR)	13.8 (NR)	-7.8 (NR)	-5.7 (NR)	-2 (-3.5 to -0.4)	0.04	Yes
Roy-Byrne, 2010[155] (G)(A)	PDSS-SR	0-28	Worse	PD	IG1	52	NR	NR	13.8 (NR)	13.8 (NR)	-8.2 (NR)	-5.4 (NR)	-2.7 (-4.3 to -1.1)	0.003	Yes
Roy-Byrne, 2010[155] (G)(A)	PDSS-SR	0-28	Worse	PD	IG1	78	NR	NR	13.8 (NR)	13.8 (NR)	-7.7 (NR)	-6.4 (NR)	-1.2 (-3 to 0.5)	0.32	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	<15 on GAD-7 at BL	IG1	26	187	60	NR	NR	NR	NR	NR	<0.05	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	<15 on PHQ-9 at BL	IG1	26	182	60	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	<4 year college	IG1	26	164	49	NR	NR	NR	NR	NR	<0.05	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	≥15 on GAD-7 at BL	IG1	26	114	41	NR	NR	NR	NR	NR	NR, NSD	Yes

Appendix F Table 9. Anxiety Symptom Severity Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	≥15 on PHQ-9 at BL	IG1	26	119	40	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	≥4 year college	IG1	26	137	52	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	Age 18-34 years	IG1	26	108	37	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	Age 35-59 years	IG1	26	149	51	NR	NR	NR	NR	NR	<0.05	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	Age 60-75 years	IG1	26	44	13	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	All	IG1	13	301	101	65.7 (14.6)	65.1 (8.7)	-6.8 (12.7)	-5.4 (8.7)	-1.4 (-4.1 to 1.3)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	All	IG1	26	301	101	65.7 (14.6)	65.1 (8.7)	-9 (13)	-6.6 (8.7)	-2.4 (-5.1 to 0.3)	0.02	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	All	IG1	52	301	101	65.7 (14.6)	65.1 (8.7)	-9 (13.1)	-7.8 (8.8)	-1.2 (-3.9 to 1.5)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	All	IG2	13	302	101	65.6 (13.7)	65.1 (8.7)	-6.4 (12.4)	-5.4 (8.7)	-1 (-3.6 to 1.6)	NR	NR
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	All	IG2	26	302	101	65.6 (13.7)	65.1 (8.7)	-8.9 (12.2)	-6.6 (8.7)	-2.3 (-4.9 to 0.3)	NR	NR
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	All	IG2	52	302	101	65.6 (13.7)	65.1 (8.7)	-9.6 (11.9)	-7.8 (8.8)	-1.8 (-4.3 to 0.7)	NR	NR

Appendix F Table 9. Anxiety Symptom Severity Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	Female	IG1	26	235	82	NR	NR	NR	NR	NR	<0.05	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	Male	IG1	26	66	19	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	nonWhite (NOS)	IG1	26	44	24	NR	NR	NR	NR	NR	<0.05	Yes
Rollman, 2018[154] (G)(A)	PROMIS-Anxiety	36.3-82.7	Worse	White	IG1	26	257	77	NR	NR	NR	NR	NR	NR, NSD	Yes
Clark, 2022[141] (G)(A)	SAD composite	NR	Worse	All	IG1	13	34	33	0.7 (0.9)	0.7 (0.7)	-1.5 (1.1)	0.1 (0.8)	-1.6 (-2 to -1.2)	<0.001	Yes
Clark, 2022[141] (G)(A)	SAD composite	NR	Worse	All	IG1	52	34	34	0.7 (0.9)	0.7 (0.7)	-2.4 (1)	-0.1 (0.8)	-2.3 (-2.7 to -1.9)	<0.001	Yes
Clark, 2022[141] (G)(A)	SAD composite	NR	Worse	All	IG2	13	34	33	0.8 (0.6)	0.7 (0.7)	-1.2 (0.7)	0.1 (0.8)	-1.2 (-1.6 to -0.8)	<0.001	Yes
Clark, 2022[141] (G)(A)	SAD composite	NR	Worse	All	IG2	52	34	34	0.8 (0.6)	0.7 (0.7)	-2.1 (0.7)	-0.1 (0.8)	-2 (-2.4 to -1.6)	<0.001	Yes
Sundquist, 2015[161] (G)(A or D)	SCL-ASS8	NR	Worse	All	IG1	8	84	89	1.3 (NR)	1.4 (NR)	-0.5 (0.6)	-0.5 (0.7)	0 (-0.2 to 0.2)	NR	NR
Stanley, 2009[158] (O)(A)	SIGH-A	0-56	Worse	All	IG1	13	65	50	19.4 (7.7)	19.1 (7.9)	-4.3 (7.6)	-3 (7.7)	-1.3 (-4.1 to 1.5)	0.23	Yes
Stanley, 2009[158] (O)(A)	SIGH-A	0-56	Worse	All	IG1	26	53	42	19.4 (7.7)	19.1 (7.9)	-4.9 (7.7)	-2.9 (8.3)	-2 (-5.2 to 1.2)	0.55	Yes

Appendix F Table 9. Anxiety Symptom Severity Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Stanley, 2009[158] (O)(A)	SIGH-A	0-56	Worse	All	IG1	39	54	42	19.4 (7.7)	19.1 (7.9)	-5.8 (7.9)	-3.2 (8.4)	-2.6 (-5.9 to 0.7)	0.55	Yes
Stanley, 2009[158] (O)(A)	SIGH-A	0-56	Worse	All	IG1	52	51	41	19.4 (7.7)	19.1 (7.9)	-6.2 (7.2)	-3.4 (7.9)	-2.8 (-5.9 to 0.3)	0.55	Yes
Stanley, 2009[158] (O)(A)	SIGH-A	0-56	Worse	All	IG1	61	52	42	19.4 (7.7)	19.1 (7.9)	-5.5 (8)	-4 (8)	-1.5 (-4.7 to 1.7)	0.55	Yes
Stanley, 2014[159] (O)(A)	SIGH-A	0-56	Worse	All	IG1	26	60	68	19.8 (8.5)	21 (9.7)	-4.5 (9.3)	-1 (10.1)	-3.5 (-6.9 to -0.1)	0.015	Yes
Roy-Byrne, 2010[155] (G)(A)	SPIN	0-68	Worse	SAnD	IG1	26	NR	NR	40.9 (NR)	41.8 (NR)	-13.5 (NR)	-7.4 (NR)	-7.1 (-12.1 to -2)	0.03	Yes
Roy-Byrne, 2010[155] (G)(A)	SPIN	0-68	Worse	SAnD	IG1	52	NR	NR	40.9 (NR)	41.8 (NR)	-15.6 (NR)	-10.8 (NR)	-5.7 (-10.7 to -0.7)	0.08	Yes
Roy-Byrne, 2010[155] (G)(A)	SPIN	0-68	Worse	SAnD	IG1	78	NR	NR	40.9 (NR)	41.8 (NR)	-16.7 (NR)	-13.1 (NR)	-4.5 (-9.7 to 0.8)	0.19	Yes
Burger, 2020[140] (Pr)(A or D)	STAI	20-80	Worse	All	IG1	g24	115	120	48.6 (8.7)	48.5 (8.4)	-0.9 (10.4)	-5.3 (9.9)	4.5 (2 to 7)	<0.001	Yes
Burger, 2020[140] (Pr)(A or D)	STAI	20-80	Worse	All	IG1	g36	98	108	48.6 (8.7)	48.5 (8.4)	-5.4 (9.8)	-7 (11.1)	1.5 (-1.2 to 4.2)	0.275	Yes
Burger, 2020[140] (Pr)(A or D)	STAI	20-80	Worse	All	IG1	p06	94	83	48.6 (8.7)	48.5 (8.4)	-7.7 (10.4)	-7.1 (11.8)	-1.4 (-4.4 to 1.5)	0.342	Yes
Burger, 2020[140] (Pr)(A or D)	STAI	20-80	Worse	All	IG1	p26 (56)	91	97	48.6 (8.7)	48.5 (8.4)	-6.5 (11.9)	-7.7 (10.4)	0.9 (-2.2 to 4.1)	0.560	Yes

Appendix F Table 9. Anxiety Symptom Severity Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Linden, 2005[150] (G)(A)	STAI	20-80	Worse	All	IG1	14.5	31	32	52.2 (11.8)	52.1 (10.5)	-7.6 (12.8)	-1.4 (11.8)	-6.2 (-12.3 to -0.1)	NR	NR
Stanley, 2014[159] (O)(A)	STAI-T	20-80	Worse	All	IG1	26	60	68	46.7 (9.1)	47.5 (9.1)	-7 (9.7)	-2.1 (10.1)	-4.8 (-8.3 to -1.4)	0.004	Yes
Vera, 2021 (G)(A)[163]	DASS-21 Anx	0-28	Worse	All	IG1	20	22	27	26.7 (11.9)	18.3 (10.2)	-13.4 (11.8)	-5.7 (10.2)	-7.7 (-13.9 to -1.6)	0.013	Yes
	DASS-21 Anx	0-28	Worse	All	IG1	28	26	29	26.7 (11.9)	18.3 (10.2)	-12.5 (12.1)	-4.7 (10.2)	-7.8 (-13.7 to -1.9)	0.013	Yes

*(G)-General adult population; (O)-Older adult population; (P) Perinatal population; (A) Study required anxiety; (A or D) Anxiety or Depression allowed.

Abbreviations: BAI = Beck Anxiety Inventory; BSI = Brief Symptom Inventory; CG = control group; CI = confidence interval; FUP = followup; GAD = Generalized Anxiety Disorder assessment; GADSS = Generalized Anxiety Disorder Severity Scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety; IG = intervention group; NOS = not otherwise specified; PD = panic disorder; PDSS-SR = Panic Disorder Severity Scale- Self Report; PROMIS-Anxiety = Patient-Reported Outcomes Measurement Information System – Anxiety; SAnD = social anxiety disorder; SCL-ASS8 = Symptom Checklist – Anxiety Symptom Scale; SD = standard deviation; SIGH-A = Structured Interview Guide for the Hamilton Anxiety Rating Scale; SPIN = Social Phobia Inventory; STAI = State Trait Anxiety Inventory.

Appendix F Table 10. Anxiety Symptom Remission and Response Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Outcome	Measure	IG	Analyzed	FUP, wks	OR (95% CI)	IG n/N (%)	CG n/N (%)	p-value	Adj
Gensichen, 2019[144] (G)(A)	Anxiety remission	BAI <11.1	IG1	All	26	2.12 (1.19 to 3.77)	44/230 (27.0)	19/189 (13.0)	NR	No
Gensichen, 2019[144] (G)(A)	Anxiety remission	BAI <11.1	IG1	All	52	2.21 (1.3 to 3.77)	54/230 (34.0)	23/189 (16.0)	NR	No
Gensichen, 2019[144] (G)(A)	Anxiety remission	No panic attacks	IG1	All	26	1.05 (0.7 to 1.56)	84/230 (48.6)	67/189 (41.9)	0.019	No
Gensichen, 2019[144] (G)(A)	Anxiety remission	No panic attacks	IG1	All	52	1.27 (0.85 to 1.9)	88/230 (53.3)	62/189 (42.2)	0.019	No
Graham, 2020[145] (G)(A or D)	Anxiety remission	Recovery from anxiety	IG1	All	8	2.24 (1.07 to 4.68)	42/74 (56.9)	27/72 (37.9)	NR	Yes
Gensichen, 2019[144] (G)(A)	Anxiety response	10.3-pt decrease in BAI	IG1	All	26	1.07 (0.69 to 1.67)	59/230 (37.0)	46/189 (31.0)	NR	No
Gensichen, 2019[144] (G)(A)	Anxiety response	10.3-pt decrease in BAI	IG1	All	52	1.29 (0.83 to 2)	66/230 (42.0)	45/189 (32.0)	NR	No
Stanley, 2014[159] (O)(A)	Anxiety response	20% reduction in sx	IG1	All	26	2.22 (1.02 to 4.8)	24/74 (32.4)	13/73 (17.8)	0.125	No
Stanley, 2009[158] (O)(A)	Anxiety response	GADSS ≥ -2.0 (meaningful change score)	IG1	All	13	1.26 (0.64 to 2.49)	38/70 (54.3)	31/64 (48.4)	NR	NR
Stanley, 2009[158] (O)(A)	Anxiety response	GADSS ≥ -2.0 (meaningful change score)	IG1	All	61	1.18 (0.59 to 2.36)	29/70 (41.4)	24/64 (37.5)	NR	NR

*(G)-General adult population; (O)-Older adult population; (P) Perinatal population; (A) Study required anxiety; (A or D) Anxiety or Depression allowed.

Abbreviations: BAI = Beck Anxiety Inventory; CI = confidence interval; CG = control group; FUP = followup; NR = not reported; GADSS = Generalized Anxiety Disorder Severity Scale; IG = intervention group; OR = odds ratio.

Appendix F Table 11. Results for Anxiety Symptoms Severity From ESRs of Psychological Treatment of Anxiety Compared to Controls (KQ4)

Author, Year	Population	Intervention	Control	Outcome	Followup	k	N analyzed	SMD (95% CI)	I^2 (%)
Cuijpers, 2016[164]	GAD	CBT	Control, nonactive	Anxiety Sx	Post-tx	31	NR	-0.80 (-0.93 to -0.67)	33
van Dis, 2019[167]	GAD	CBT	Any	Anxiety Sx	FUP 52+	10	NR	-0.22 (-0.42 to -0.02)	18
	GAD	CBT	Any	Anxiety Sx	FUP 4-26	3	NR	-0.07 (-0.63 to 0.50)	73
	GAD	CBT	Any	Anxiety Sx	FUP 26-52	11	NR	-0.40 (-0.67 to -0.13)	59
Cuijpers, 2016[164]	GAD (Adjusted for publication bias)	CBT	Control, nonactive	Anxiety Sx	Post-tx	42	NR	-0.59 (-0.75 to -0.44)	62
	GAD (Low RoB only)	CBT	Control, nonactive	Anxiety Sx	Post-tx	9	NR	-0.82 (-1.04 to -0.60)	46
	SAnD	CBT	Control, nonactive	Anxiety Sx	Post-tx	48	NR	-0.88 (-1.03 to -0.74)	64
van Dis, 2019[167]	SAnD	CBT	Any	Anxiety Sx	FUP 52+	3	NR	-0.42 (-0.79 to -0.04)	0
	SAnD	CBT	Any	Anxiety Sx	FUP 4-26	4	NR	-0.60 (-0.85 to -0.36)	0
	SAnD	CBT	Any	Anxiety Sx	FUP 26-52	3	NR	-0.34 (-0.61 to -0.07)	0
Cuijpers, 2016[164]	SAnD (Low RoB only)	CBT	Control, nonactive	Anxiety Sx	Post-tx	8	NR	-0.76 (-1.06 to -0.47)	71
Cuijpers, 2016[164]	PD	CBT	Control, nonactive	Anxiety Sx	Post-tx	42	NR	-0.81 (-1.04 to -0.59)	77
van Dis, 2019[167]	PD	CBT	Any	Anxiety Sx	FUP 52+	5	NR	-0.14 (-0.47 to 0.19)	0
	PD	CBT	Any	Anxiety Sx	FUP 4-26	6	NR	-0.27 (-0.55 to 0.01)	8
	PD	CBT	Any	Anxiety Sx	FUP 26-52	9	NR	-0.35 (-0.59 to -0.11)	12
Cuijpers, 2016[164]	PD (Low RoB only)	CBT	Control, nonactive	Anxiety Sx	Post-tx	4	NR	-0.61 (-0.96 to -0.27)	26

Appendix F Table 11. Results for Anxiety Symptoms Severity From ESRs of Psychological Treatment of Anxiety Compared to Controls (KQ4)

Author, Year	Population	Intervention	Control	Outcome	Followup	k	N analyzed	SMD (95% CI)	I^2 (%)
Gould, 2012[165]	Older adults	CBT	Control, nonactive	Anxiety Sx	Post-tx	7	215	-0.66 (-0.94 to -0.38)	0.0
	Older adults	CBT	Control, active	Anxiety Sx	Post-tx	7	348	-0.20 (-0.42 to 0.01)	0.0
	Older adults	CBT	Control, active	Anxiety Sx	52	3	172	-0.21 (-0.76 to 0.35)	65.1
	Older adults	CBT	Control, active	Anxiety Sx	26	4	202	-0.29 (-0.57 to -0.01)	0.0
	Older adults	CBT	Control, active	Anxiety Sx	13	3	164	-0.40 (-0.91 to 0.12)	55.1
Li, 2022[84]	Perinatal	CBT	Any	Anxiety Sx	Post-tx	13	919	-0.79 (-1.16 to -0.43)	85
	Perinatal	CBT	Any	Anxiety Sx	Long-term (~12 months)	33	3063	-0.63 (-0.83 to -0.43)	84

Abbreviations: CBT = cognitive behavioral therapy; FUP = followup; GAD = generalized anxiety disorder; NR = not reported; PD = panic disorder; RoB = risk of bias; SAnD = social anxiety disorder SMD = standardized mean difference; Sx = symptoms; Tx = treatment.

Appendix F Table 12. Other Mental Health Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Corpas, 2021 (G)(A or D)[142]	Depression symptoms	PHQ-9	0-27	Worse	All	IG1	8	53	52	12.8 (3.8)	13.4 (3.5)	-3 (4.1)	-1.4 (3.3)	-1.6 (-3.1 to -0.2)	0.041	NR
King, 2000[147] (G)(A or D)	Depression symptoms	BDI	0-63	Worse	All	IG1	17	56	62	27.6 (8.4)	26.5 (8.9)	-14.9 (9)	-9.3 (10.7)	-5.6 (-9.2 to -2)	NR	NR
King, 2000[147] (G)(A or D)	Depression symptoms	BDI	0-63	Worse	All	IG1	52	50	57	27.6 (8.4)	26.5 (8.9)	-18.3 (8.6)	-16.3 (8.7)	-2 (-5.3 to 1.3)	NR	NR
King, 2000[147] (G)(A or D)	Depression symptoms	BDI	0-63	Worse	All	IG2	17	62	62	25.4 (8.6)	26.5 (8.9)	-13.9 (8.2)	-9.3 (10.7)	-4.6 (-8 to -1.2)	NR	NR
King, 2000[147] (G)(A or D)	Depression symptoms	BDI	0-63	Worse	All	IG2	52	58	57	25.4 (8.6)	26.5 (8.9)	-14.3 (9)	-16.3 (8.7)	2 (-1.2 to 5.2)	NR	NR
Proudfoot, 2004[153] (G)(A or D)	Depression symptoms	BDI	0-63	Worse	All	IG1	8	95	100	24.9 (10.8)	24.7 (9.2)	-12.8 (10.1)	-6.3 (10.2)	-6.5 (-9.3 to -3.7)	0.35	Yes
Proudfoot, 2004[153] (G)(A or D)	Depression symptoms	BDI	0-63	Worse	All	IG1	13	93	85	24.9 (10.8)	24.7 (9.2)	-12.8 (10.6)	-8.3 (10.2)	-4.5 (-7.6 to -1.4)	0.35	Yes
Proudfoot, 2004[153] (G)(A or D)	Depression symptoms	BDI	0-63	Worse	All	IG1	21	83	81	24.9 (10.8)	24.7 (9.2)	-15.3 (9.8)	-11.2 (9.8)	-4.1 (-7.1 to -1.1)	0.35	Yes
Proudfoot, 2004[153] (G)(A or D)	Depression symptoms	BDI	0-63	Worse	All	IG1	34	94	92	24.9 (10.8)	24.7 (9.2)	-15.6 (9.9)	-9.8 (10.4)	-5.8 (-8.7 to -2.9)	0.35	Yes
Stanley, 2009[158] (O)(A)	Depression symptoms	BDI-II	0-63	Worse	All	IG1	13	65	50	16.3 (8)	16.4 (9.5)	-6.1 (7.5)	-3.6 (9)	-2.5 (-5.5 to 0.5)	0.02	Yes
Stanley, 2009[158] (O)(A)	Depression symptoms	BDI-II	0-63	Worse	All	IG1	26	53	42	16.3 (8)	16.4 (9.5)	-7 (7.6)	-5.5 (9)	-1.5 (-4.8 to 1.8)	0.16	Yes
Stanley, 2009[158]	Depression symptoms	BDI-II	0-63	Worse	All	IG1	39	54	42	16.3 (8)	16.4 (9.5)	-6.6 (7.6)	-6.1 (8.5)	-0.5 (-3.7 to	0.16	Yes

Appendix F Table 12. Other Mental Health Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
(O)(A)														2.7)		
Stanley, 2009[158] (O)(A)	Depression symptoms	BDI-II	0-63	Worse	All	IG1	52	51	41	16.3 (8)	16.4 (9.5)	-7.8 (7.5)	-6.3 (8.5)	-1.5 (-4.8 to 1.8)	0.16	Yes
Stanley, 2009[158] (O)(A)	Depression symptoms	BDI-II	0-63	Worse	All	IG1	61	52	42	16.3 (8)	16.4 (9.5)	-8 (7.7)	-5 (8.6)	-3 (-6.3 to 0.3)	0.16	Yes
Lang, 2006[149] (G)(A or D)	Depression symptoms	BSI-D	0-72	Worse	All	IG1	4	25	27	69.9 (8.8)	68.7 (8.2)	-7.9 (10.2)	-1.5 (8.4)	-6.4 (-11.5 to -1.3)	NR	NR
Lang, 2006[149] (G)(A or D)	Depression symptoms	BSI-D	0-72	Worse	All	IG1	16	22	25	69.9 (8.8)	68.7 (8.2)	-7.6 (8.9)	-2 (8.4)	-5.6 (-10.5 to -0.7)	NR	NR
Lang, 2006[149] (G)(A or D)	Depression symptoms	BSI-D	0-72	Worse	All	IG1	30	21	25	69.9 (8.8)	68.7 (8.2)	-2.7 (9.1)	-3 (8.5)	0.3 (-4.8 to 5.4)	<0.001	NR
Burger, 2020[140] (Pr)(A or D)	Depression symptoms	EPDS	0-30	Worse	All	IG1	g24	120	120	9.8 (4.1)	9.7 (4.1)	0.6 (4.6)	-0.5 (4.4)	1.2 (0.2 to 2.1)	0.015	Yes
Burger, 2020[140] (Pr)(A or D)	Depression symptoms	EPDS	0-30	Worse	All	IG1	g36	97	104	9.8 (4.1)	9.7 (4.1)	-0.4 (4.4)	-1.4 (4.4)	0.8 (-0.2 to 1.8)	0.136	Yes
Burger, 2020[140] (Pr)(A or D)	Depression symptoms	EPDS	0-30	Worse	All	IG1	p06	90	88	9.8 (4.1)	9.7 (4.1)	-1.4 (4.4)	-1.3 (4.6)	-0.1 (-1.2 to 1)	0.844	Yes
Burger, 2020[140] (Pr)(A or D)	Depression symptoms	EPDS	0-30	Worse	All	IG1	p26 (56)	87	95	9.8 (4.1)	9.7 (4.1)	-1.8 (4.8)	-1.4 (4.8)	-0.3 (-1.6 to 1)	0.647	Yes
O'Mahen, 2022 (Pr)(A)	Depression symptoms	EPDS	0-30	Worse	All	IG1	10	45	51	13.6 (4.5)	11.4 (5.2)	-3.2 (4.4)	-0.9 (5.2)	-2.3 (-4.3 to -0.4)	<0.05	NR
O'Mahen, 2022 (Pr)(A)	Depression symptoms	EPDS	0-30	Worse	All	IG1	18	45	51	13.6 (4.5)	11.4 (5.2)	-4.2 (4.6)	-1.9 (5.2)	-2.3 (-4.3 to -0.3)	<0.05	NR

Appendix F Table 12. Other Mental Health Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
O'Mahen, 2022 (Pr)(A)	Depression symptoms	EPDS	0-30	Worse	All	IG1	34 (34)	45	51	13.6 (4.5)	11.4 (5.2)	-5.7 (4.7)	-3 (5.1)	-2.7 (-4.7 to -0.8)	<0.01	NR
Suchan, 2022 (PP)(A or D)	Depression symptoms	EPDS	0-30	Worse	All	IG1	8	25	29	14.5 (4.3)	15.4 (4.8)	-4.9 (5.1)	-3.1 (4.9)	-1.8 (-4.5 to 0.8)	NR	NR
Suchan, 2022 (PP)(A or D)	Depression symptoms	EPDS	0-30	Worse	All	IG1	13 (NR)	24	30	14.5 (4.3)	15.4 (4.8)	-5.7 (4.3)	-3.9 (5.4)	-1.8 (-4.5 to 0.8)	NR	NR
Fletcher, 2005[143] (G)(A or D)	Depression symptoms	HADS-D	0-21	Worse	All	IG1	12	15	15	8.9 (2.2)	7.9 (3)	-1.4 (3.3)	-1.6 (3)	0.2 (-2.1 to 2.5)	0.349	NR
Lam, 2010[148] (O)(A or D)	Depression symptoms	HADS-D	0-21	Worse	All	IG1	6	149	150	4.9 (4.4)	3.9 (3.5)	0.4 (4)	0.8 (4.2)	0 (-0.7 to 0.7)	0.972	Yes
Lam, 2010[148] (O)(A or D)	Depression symptoms	HADS-D	0-21	Worse	All	IG1	12	149	150	4.9 (4.4)	3.9 (3.5)	0.6 (4.1)	0.9 (4.3)	0 (-0.7 to 0.7)	0.972	Yes
Lam, 2010[148] (O)(A or D)	Depression symptoms	HADS-D	0-21	Worse	All	IG1	26	149	150	4.9 (4.4)	3.9 (3.5)	0.7 (4.3)	0.9 (4.6)	0 (-0.7 to 0.7)	0.972	Yes
Lam, 2010[148] (O)(A or D)	Depression symptoms	HADS-D	0-21	Worse	All	IG1	52	149	150	4.9 (4.4)	3.9 (3.5)	1.1 (4.6)	1.4 (4.6)	0 (-0.7 to 0.7)	0.972	Yes
Schreuders, 2007[156] (G)(A or D)	Depression symptoms	HADS-D	0-21	Worse	All	IG1	13	61	69	7.1 (3.8)	7.7 (4)	-1.9 (3.8)	-1.3 (3.6)	-0.7 (-1.9 to 0.6)	0.123	Yes
Sundquist, 2015[161] (G)(A or D)	Depression symptoms	HADS-D	0-21	Worse	All	IG1	8	83	86	8.5 (3.6)	9.3 (3.7)	NR	NR	0.3 (-0.9 to 1.5)	0.59	No
Seekles, 2011[157] (G)(A or D)	Depression symptoms	IDS	0-79	Worse	All	IG1	8	55	53	29.5 (11.3)	31.8 (10.3)	-4.2 (7.5)	-4.5 (7.5)	0.2 (-2.6 to 3.1)	0.30	No

Appendix F Table 12. Other Mental Health Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Nordgren, 2014[151] (G)(A)	Depression symptoms	MADRS	0-60	Worse	All	IG1	10	50	50	19.6 (6.8)	17.8 (6.8)	-8.8 (7.1)	-1.9 (7.1)	-6.9 (-9.7 to -4.1)	<0.001	NR
Sundquist, 2015[161] (G)(A or D)	Depression symptoms	MADRS	0-60	Worse	All	IG1	8	81	86	20 (7.7)	22 (6.9)	NR	NR	-0.7 (-3.2 to 1.8)	0.60	No
Roy-Byrne, 2010[155] (G)(A)	Depression symptoms	PHQ-8	NR	Worse	All	IG1	26	503	501	12.6 (6.8)	12.5 (6)	-5.1 (5.9)	-3.4 (6.2)	-1.7 (-2.4 to -1)	0.002	No
Roy-Byrne, 2010[155] (G)(A)	Depression symptoms	PHQ-8	NR	Worse	All	IG1	52	503	501	12.6 (6.8)	12.5 (6)	-6 (6.4)	-3.6 (6.4)	-2.4 (-3.2 to -1.6)	<0.001	No
Roy-Byrne, 2010[155] (G)(A)	Depression symptoms	PHQ-8	NR	Worse	All	IG1	78	503	501	12.6 (6.8)	12.5 (6)	-6.1 (6)	-4.6 (6.2)	-1.6 (-2.3 to -0.8)	0.006	No
Stanley, 2014[159] (O)(A)	Depression symptoms	PHQ-8	0-24	Worse	All	IG1	26	60	68	9.9 (5.7)	10 (5.4)	-3.7 (5.7)	-0.8 (5.8)	-2.9 (-4.9 to -0.9)	0.002	Yes
Clark, 2022 (G)(A)	Depression symptoms	PHQ-9	0-27	Worse	All	IG1	13	34	33	6.8 (5.1)	8.4 (5)	-4.4 (4.4)	0.3 (5.4)	5.8 (4 to 7.5)	<0.001	Yes
Clark, 2022 (G)(A)	Depression symptoms	PHQ-9	0-27	Worse	All	IG1	52	34	34	6.8 (5.1)	8.4 (5)	-5.4 (4.5)	-0.2 (5.2)	6.3 (4.5 to 8)	<0.001	Yes
Clark, 2022 (G)(A)	Depression symptoms	PHQ-9	0-27	Worse	All	IG2	13	34	33	9.2 (5.8)	8.4 (5)	-3.7 (5.1)	0.3 (5.4)	3.5 (1.7 to 5.2)	<0.001	Yes
Clark, 2022 (G)(A)	Depression symptoms	PHQ-9	0-27	Worse	All	IG2	52	34	34	9.2 (5.8)	8.4 (5)	-5.4 (5)	-0.2 (5.2)	4.7 (2.9 to 6.4)	<0.001	Yes
Corpas, 2021 (G)(A or D)	Depression symptoms	PHQ-9	0-27	Worse	All	IG1	8	53	52	12.8 (3.8)	13.4 (3.5)	-3 (4.1)	-1.4 (3.3)	-1.6 (-3.1 to -0.2)	0.041	NR
Gensichen, 2019[144] (G)(A)	Depression symptoms	PHQ-9	0-27	Worse	All	IG1	26	230	189	11.2 (5.8)	11.2 (5.6)	-3.8 (5.2)	-1.8 (5.6)	-2 (-3.1 to -0.9)	<0.001	No
Gensichen, 2019[144] (G)(A)	Depression symptoms	PHQ-9	0-27	Worse	All	IG1	52	230	189	11.2 (5.8)	11.2 (5.6)	-4.7 (5)	-2.3 (5.8)	-2.4 (-3.6 to -1.3)	<0.001	No

Appendix F Table 12. Other Mental Health Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Graham, 2020[145] (G)(A or D)	Depression symptoms	PHQ-9	0-27	Worse	All	IG1	4	74	72	14 (43)	13.6 (44.1)	-5 (43)	-1.7 (45.9)	2.9 (1.3 to 4.5)	NR	No
Graham, 2020[145] (G)(A or D)	Depression symptoms	PHQ-9	0-27	Worse	All	IG1	8	74	72	14 (43)	13.6 (44.1)	-6.8 (45.3)	-2.2 (51.1)	4.4 (2.7 to 6)	NR	No
Sundquist, 2015[161] (G)(A or D)	Depression symptoms	PHQ-9	0-27	Worse	All	IG1	8	82	85	13 (6)	14 (5.2)	NR	NR	-0.2 (-2 to 1.6)	0.84	No
Torres-Platas, 2019[162] (O)(A or D)	Depression symptoms	PHQ-9	0-27	Worse	All	IG1	8	27	26	14.8 (4.9)	15.7 (5.1)	-7.9 (4.4)	-4 (4.7)	-3.9 (-6.4 to -1.4)	0.002	No
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	<15 on GAD-7 at BL	IG1	26	187	60	NR	NR	NR	NR	NR	<0.05	NR
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	<15 on PHQ-9 at BL	IG1	26	182	60	NR	NR	NR	NR	NR	NR, NSD	NR
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	<4 year college	IG1	26	164	49	NR	NR	NR	NR	NR	<0.05	NR
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	≥15 on GAD-7 at BL	IG1	26	114	41	NR	NR	NR	NR	NR	NR, NSD	NR
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	≥15 on PHQ-9 at BL	IG1	26	119	40	NR	NR	NR	NR	NR	<0.05	NR
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	≥4 year college	IG1	26	137	52	NR	NR	NR	NR	NR	NR, NSD	NR
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	Age 18-34 years	IG1	26	108	37	NR	NR	NR	NR	NR	NR, NSD	NR

Appendix F Table 12. Other Mental Health Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	Age 35-59 years	IG1	26	149	51	NR	NR	NR	NR	NR	<0.05	NR
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	Age 60-75 years	IG1	26	44	13	NR	NR	NR	NR	NR	NR, NSD	NR
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	All	IG1	13	301	101	62.3 (16.8)	61.2 (7.2)	-6.7 (15.5)	-6 (8.1)	-0.7 (-3.9 to 2.5)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	All	IG1	26	301	101	62.3 (16.8)	61.2 (7.2)	-8.9 (14.7)	-6.5 (8.1)	-2.4 (-5.4 to 0.6)	0.006	Yes
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	All	IG1	52	301	101	62.3 (16.8)	61.2 (7.2)	-9 (14.8)	-7.5 (8.1)	-1.5 (-4.5 to 1.5)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	All	IG2	13	302	101	61.8 (14.2)	61.2 (7.2)	-6.3 (14)	-6 (8.1)	-0.3 (-3.2 to 2.6)	NR	NR
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	All	IG2	26	302	101	61.8 (14.2)	61.2 (7.2)	-8.8 (12.3)	-6.5 (8.1)	-2.3 (-4.9 to 0.3)	NR	NR
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	All	IG2	52	302	101	61.8 (14.2)	61.2 (7.2)	-8.9 (12.5)	-7.5 (8.1)	-1.4 (-4 to 1.2)	NR	NR
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	Female	IG1	26	235	82	NR	NR	NR	NR	NR	<0.05	Yes
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	Male	IG1	26	66	19	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	Non-White (NOS)	IG1	26	44	24	NR	NR	NR	NR	NR	<0.05	Yes
Rollman, 2018[154]	Depression symptoms	PROMIS-Depression	37.1-81.1	Worse	White	IG1	26	257	77	NR	NR	NR	NR	NR	NR, NSD	Yes

Appendix F Table 12. Other Mental Health Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
(G)(A)																
Sundquist, 2015[161]	Depression symptoms	SCL-D6	NR	Worse	All	IG1	8	84	89	2.1 (NR)	2.3 (NR)	-0.9 (0.8)	-0.9 (0.8)	0.1 (-0.2 to 0.3)	NR	NR
Vera, 2021 (G)(A)[163]	Depression symptoms	DASS-21 Dep	0-28	Worse	All	IG1	20	22	27	24 (11.3)	17.2 (8.4)	-13.4 (10.7)	-4.4 (9.3)	-9 (-14.6 to -3.4)	NR	NR
	Depression symptoms	DASS-21 Dep	0-28	Worse	All	IG1	28	26	29	24 (11.3)	17.2 (8.4)	-10.9 (11.4)	-4.4 (9.1)	-6.4 (-11.8 to -1)	NR	NR
	Depression symptoms	PHQ-9	0-27	Worse	All	IG1	28	25	26	16.1 (4.7)	12.1 (5.2)	-6.2 (5.9)	-1 (5.5)	-5.2 (-8.3 to -2)	NR	NR
King, 2000[147] (G)(A or D)	Global mental health symptoms	BSI	0-4	Worse	All	IG1	17	51	56	NR	NR	NR	NR	NR	NR	NR
King, 2000[147] (G)(A or D)	Global mental health symptoms	BSI	0-4	Worse	All	IG1	52	46	53	NR	NR	NR	NR	NR	NR	NR
King, 2000[147] (G)(A or D)	Global mental health symptoms	BSI	0-4	Worse	All	IG2	17	62	56	NR	NR	NR	NR	NR	NR	NR
King, 2000[147] (G)(A or D)	Global mental health symptoms	BSI	0-4	Worse	All	IG2	52	56	53	NR	NR	NR	NR	NR	NR	NR
Kendrick, 2005[146] (G)(A or D)	Global mental health symptoms	CIS-R	0-57	Worse	All	IG1	8	90	78	NR	NR	FU=15 (11.4)	FU=13.8 (13.9)	-1.2 (-5.2 to 2.8)	0.551	Yes

Appendix F Table 12. Other Mental Health Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Kendrick, 2005[146] (G)(A or D)	Global mental health symptoms	CIS-R	0-57	Worse	All	IG1	26	90	78	NR	NR	FU=12.8 (12)	FU=10.1 (10.9)	-1.1 (-2.9 to 5.1)	0.579	Yes
Kendrick, 2005[146] (G)(A or D)	Global mental health symptoms	CIS-R	0-57	Worse	All	IG2	8	79	78	NR	NR	FU=16.9 (12.1)	FU=13.8 (13.9)	1.4 (-2.8 to 5.6)	0.509	Yes
Kendrick, 2005[146] (G)(A or D)	Global mental health symptoms	CIS-R	0-57	Worse	All	IG2	26	79	78	NR	NR	FU=10.4 (9.4)	FU=10.1 (10.9)	-1.4 (-5.5 to 2.8)	0.510	Yes
Kendrick, 2005[146] (G)(A or D)	Global mental health symptoms	CIS-R	0-57	Worse	Moderate or severe depressive episode	IG1	8	23	23	NR	NR	FU=23.6 (13.3)	FU=20.9 (15.7)	-2.4 (-15.3 to 10.4)	0.698	Yes
Kendrick, 2005[146] (G)(A or D)	Global mental health symptoms	CIS-R	0-57	Worse	Moderate or severe depressive episode	IG1	26	23	23	NR	NR	FU=21.9 (15.7)	FU=14.2 (13)	8.9 (-8.3 to 26)	0.295	Yes
Kendrick, 2005[146] (G)(A or D)	Global mental health symptoms	CIS-R	0-57	Worse	Moderate or severe depressive episode	IG2	8	31	23	NR	NR	FU=21.5 (12)	FU=20.9 (15.7)	-5.4 (-19 to 8.3)	0.425	Yes
Kendrick, 2005[146] (G)(A or D)	Global mental health symptoms	CIS-R	0-57	Worse	Moderate or severe depressive episode	IG2	26	31	23	NR	NR	FU=13.8 (11.3)	FU=14.2 (13)	-0.8 (-18.1 to 16.5)	0.928	Yes
Fletcher, 2005[143] (G)(A or D)	Global mental health symptoms	CORE	0-136	Worse	All	IG1	12	15	15	52.3 (16.8)	50.8 (17.3)	-14.8 (17.6)	-15.3 (18.6)	0.4 (-12.5 to 13.4)	0.783	NR
Nordgren, 2014[151] (G)(A)	Global mental health	CORE-OM	0-40	Worse	All	IG1	10	50	50	18.4 (4.5)	17.6 (4.5)	-7.5 (4.9)	0 (4.5)	-7.5 (-9.3 to -5.6)	<0.001	NR

Appendix F Table 12. Other Mental Health Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
	symptoms															
Kendrick, 2005[146] (G)(A or D)	Global mental health symptoms	GHQ-12	0-100	Worse	All	IG1	8	90	78	NR	NR	FU=2.8 (4)	FU=3.5 (4.3)	-1.2 (-2.8 to 0.4)	0.131	Yes
Kendrick, 2005[146] (G)(A or D)	Global mental health symptoms	GHQ-12	0-100	Worse	All	IG1	26	90	78	NR	NR	FU=2.3 (3.4)	FU=2.9 (3.9)	-0.8 (-2.2 to 0.6)	0.243	Yes
Kendrick, 2005[146] (G)(A or D)	Global mental health symptoms	GHQ-12	0-100	Worse	All	IG2	8	79	78	NR	NR	FU=3.2 (4.4)	FU=3.5 (4.3)	-0.7 (-2.4 to 0.9)	0.398	Yes
Kendrick, 2005[146] (G)(A or D)	Global mental health symptoms	GHQ-12	0-100	Worse	All	IG2	26	79	78	NR	NR	FU=1.8 (3)	FU=2.9 (3.9)	-1.1 (-2.6 to 0.4)	0.167	Yes
Sundquist, 2015[161] (G)(A or D)	Global mental health symptoms	GSI	0-71	Worse	All	IG1	8	84	89	73 (NR)	75 (NR)	-6.4 (7.3)	-6.1 (8.5)	-0.3 (-2.7 to 2.1)	0.76	NR

*(G)-General adult population; (O)-Older adult population; (P) Perinatal population; (A) Study required anxiety; (A or D) Anxiety or Depression allowed.

Abbreviations: Adj = adjusted; BDI = Beck Depression Inventory; BL = baseline; BSI–D = Brief Symptom Inventory–Depression; CG = control group; Chg = change; CI = confidence interval; CIS–R = Clinical Interview Schedule-Revised; CORE-OM = Clinical Outcomes in Routine Evaluation-Outcome Measure; DASS-21 = Depression, Anxiety and Stress Scale - 21 Items; Diff = difference; EPDS = Edinburgh Postnatal Depression Scale; FUP = followup; GAD = Generalized Anxiety Disorder scale; GHQ = General Health Questionnaire; GSI = Global Severity Index; HADS-D = Hospital Anxiety and Depression Scale–Depression; IDS = Inventory of Depressive Symptomatology; IG = intervention group; MADRS = Montgomery–Asberg Depression Rating Scale; NOS = not otherwise specified; NR = not reported; NSD = no significant difference; PHQ = Patient Health Questionnaire; PROMIS–Depression = Patient-Reported Outcomes Measurement Information System–Depression; SCL-D6 = Symptom Checklist–Core Depression; SD = standard deviation.

Appendix F Table 13. Quality of Life Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
O'Mahen, 2022 (Pr)(A)	DAS	0-69	Better	All	IG1	10	45	51	119 (16.8)	120.3 (15.4)	-0.6 (20.8)	0.6 (18.1)	-1.2 (-9 to 6.6)	NR	NR
O'Mahen, 2022 (Pr)(A)	DAS	0-69	Better	All	IG1	18	45	51	119 (16.8)	120.3 (15.4)	-0.2 (20.8)	-1.6 (16.1)	1.4 (-6 to 8.8)	NR	NR
O'Mahen, 2022 (Pr)(A)	DAS	0-69	Better	All	IG1	34 (34)	45	51	119 (16.8)	120.3 (15.4)	-1.9 (18.8)	-4.4 (19.8)	2.5 (-5.2 to 10.3)	NR	NR
Suchan, 2022 (PP)(A or D)	DAS	0-36	Better	All	IG1	8	25	29	22 (3.7)	25.5 (5.2)	1.4 (3.8)	-0.5 (5.3)	1.9 (-0.6 to 4.4)	NR	NR
Suchan, 2022 (PP)(A or D)	DAS	0-36	Better	All	IG1	13 (NR)	24	30	22 (3.7)	25.5 (5.2)	0.9 (4)	0.2 (5.4)	0.6 (-2 to 3.2)	NR	NR
O'Mahen, 2022 (Pr)(A)	EQ-5D	0-25	Worse	All	IG1	10	45	51	7 (1.4)	6.6 (1.3)	0.2 (1.3)	0.3 (1.5)	-0.1 (-0.6 to 0.5)	NR	NR
O'Mahen, 2022 (Pr)(A)	EQ-5D	0-25	Worse	All	IG1	18	45	51	7 (1.4)	6.6 (1.3)	0.5 (1.5)	0.4 (1.7)	0.1 (-0.6 to 0.7)	NR	NR
O'Mahen, 2022 (Pr)(A)	EQ-5D	0-25	Worse	All	IG1	34 (34)	45	51	7 (1.4)	6.6 (1.3)	-0.6 (1.4)	-0.8 (1.2)	0.1 (-0.4 to 0.6)	NR	NR
Torres-Platas, 2019[162] (O)(A or D)	EQ-5D	0-25	Worse	All	IG1	8	27	26	10.3 (3.2)	9.5 (3.2)	-0.6 (3.5)	0.4 (2)	-1 (-2.5 to 0.5)	0.048	No
King, 2000[147] (G)(A or D)	EuroQoL	1.0 to -0.594	Better	All	IG1	17	50	57	NR	NR	NR	NR	NR	NR	NR
King, 2000[147] (G)(A or D)	EuroQoL	1.0 to -0.594	Better	All	IG1	52	47	54	NR	NR	NR	NR	NR	NR	NR
King, 2000[147] (G)(A or D)	EuroQoL	1.0 to -0.594	Better	All	IG2	17	62	57	NR	NR	NR	NR	NR	NR	NR
King, 2000[147] (G)(A or D)	EuroQoL	1.0 to -0.594	Better	All	IG2	52	57	54	NR	NR	NR	NR	NR	NR	NR

Appendix F Table 13. Quality of Life Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Suchan, 2022[160] (PP)(A or D)	PBQ	0-125	Worse	All	IG1	8	25	29	17.2 (10.4)	18.7 (12.8)	-5.2 (9.2)	-4.4 (11.7)	-0.8 (-6.4 to 4.9)	NR	NR
Suchan, 2022 (PP)(A or D)	PBQ	0-125	Worse	All	IG1	13 (NR)	24	30	17.2 (10.4)	18.7 (12.8)	-6.7 (9)	-6.4 (11.5)	-0.3 (-5.9 to 5.3)	NR	NR
Nordgren, 2014[151] (G)(A)	QOLI	NR	Better	All	IG1	10	50	50	0.4 (1.6)	0.9 (1.6)	0.9 (1.6)	0.2 (1.6)	0.7 (0.1 to 1.3)	<0.05	NR
Lang, 2006[149] (G)(A or D)	SF-12 MCS	0-100	Better	All	IG1	4	25	27	30.5 (10.9)	35.6 (10.9)	10.6 (11.4)	2.5 (10.6)	8.1 (2.1 to 14.1)	NR	NR
Lang, 2006[149] (G)(A or D)	SF-12 MCS	0-100	Better	All	IG1	16	22	25	30.5 (10.9)	35.6 (10.9)	12.1 (11.1)	2.3 (10.3)	9.8 (3.7 to 15.9)	NR	NR
Lang, 2006[149] (G)(A or D)	SF-12 MCS	0-100	Better	All	IG1	30	21	25	30.5 (10.9)	35.6 (10.9)	8.9 (13.1)	2.6 (10.6)	6.3 (-0.5 to 13.1)	0.001	NR
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	<15 on GAD-7 at BL	IG1	26	187	60	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	<15 on PHQ-9 at BL	IG1	26	182	61	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	<4 year college	IG1	26	164	49	NR	NR	NR	NR	NR	<0.05	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	≥15 on GAD-7 at BL	IG1	26	114	41	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	≥15 on PHQ-9 at BL	IG1	26	114	41	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	≥4 year college	IG1	26	137	52	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 18-34 years	IG1	13	108	37	30.5 (19.1)	28.5 (9.7)	6.1 (18)	11 (10)	-4.9 (-11 to	NR, NSD	Yes

Appendix F Table 13. Quality of Life Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
													1.2)		
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 18-34 years	IG1	26	108	37	30.5 (19.1)	28.5 (9.7)	12 (17.9)	13.3 (10)	-1.3 (-7.4 to 4.8)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 18-34 years	IG1	52	108	37	30.5 (19.1)	28.5 (9.7)	11.8 (16.5)	15.7 (10.1)	-3.9 (-9.6 to 1.8)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 18-34 years	IG2	13	111	37	31.1 (21)	28.5 (9.7)	8.8 (18.9)	11 (10)	-2.2 (-8.6 to 4.2)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 18-34 years	IG2	26	111	37	31.1 (21)	28.5 (9.7)	12.6 (20.4)	13.3 (10)	-0.7 (-7.6 to 6.2)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 18-34 years	IG2	52	111	37	31.1 (21)	28.5 (9.7)	12.9 (18.6)	15.7 (10.1)	-2.8 (-9.1 to 3.5)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 35-59 years	IG1	13	149	51	30.9 (11.5)	31.6 (10)	10.4 (14.7)	8.9 (10)	1.5 (-2.8 to 5.8)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 35-59 years	IG1	26	149	51	30.9 (11.5)	31.6 (10)	14.5 (27.3)	8.5 (10.1)	6 (-1.7 to 13.7)	<0.01	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 35-59 years	IG1	52	149	51	30.9 (11.5)	31.6 (10)	14.7 (24.1)	9.8 (10.1)	4.9 (-1.9 to 11.7)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 35-59 years	IG2	13	143	51	30.5 (9.8)	31.6 (10)	9.1 (10.6)	8.9 (10)	0.2 (-3.1 to 3.5)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 35-59 years	IG2	26	143	51	30.5 (9.8)	31.6 (10)	12 (18.8)	8.5 (10.1)	3.5 (-1.9 to 8.9)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 35-59 years	IG2	52	143	51	30.5 (9.8)	31.6 (10)	12 (15.4)	9.8 (10.1)	2.2 (-2.3 to 6.7)	NR, NSD	Yes

Appendix F Table 13. Quality of Life Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 60-75 years	IG1	13	37	13	34.1 (9)	35.9 (9.1)	6.8 (9.3)	9.7 (9.1)	-2.9 (-8.8 to 3)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 60-75 years	IG1	26	37	13	34.1 (9)	35.9 (9.1)	6 (9.2)	10.2 (9.3)	-4.2 (-10 to 1.6)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 60-75 years	IG1	52	37	13	34.1 (9)	35.9 (9.1)	8.7 (9.3)	14.1 (9.3)	-5.4 (-11.3 to 0.5)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 60-75 years	IG2	13	51	13	36.4 (10.1)	35.9 (9.1)	6.8 (10.4)	9.7 (9.1)	-2.9 (-9.1 to 3.3)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 60-75 years	IG2	26	51	13	36.4 (10.1)	35.9 (9.1)	11 (10.3)	10.1 (9.3)	0.9 (-5.3 to 7.1)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Age 60-75 years	IG2	52	51	13	36.4 (10.1)	35.9 (9.1)	11.5 (10.4)	14.1 (9.3)	-2.6 (-8.8 to 3.6)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	All	IG1	13	301	101	31.9 (15.5)	31.8 (10.8)	9.1 (14.5)	9.8 (10.9)	-0.7 (-3.8 to 2.4)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	All	IG1	26	301	101	31.9 (15.5)	31.8 (10.8)	12.3 (21.7)	10.4 (11.2)	1.9 (-2.5 to 6.3)	0.15	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	All	IG1	52	301	101	31.9 (15.5)	31.8 (10.8)	12.7 (17)	12.3 (11)	0.4 (-3.1 to 3.9)	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	All	IG2	13	302	101	32.4 (17.7)	31.8 (10.8)	8.5 (16)	9.8 (10.9)	-1.3 (-4.7 to 2.1)	NR	NR
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	All	IG2	26	302	101	32.4 (17.7)	31.8 (10.8)	12 (22.8)	10.4 (11.2)	1.6 (-3 to 6.2)	NR	NR

Appendix F Table 13. Quality of Life Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	All	IG2	52	302	101	32.4 (17.7)	31.8 (10.8)	12.3 (17.7)	12.3 (11)	0 (-3.7 to 3.7)	NR	NR
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Female	IG1	26	235	82	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Male	IG1	26	66	19	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	Non-White (NOS)	IG1	26	44	27	NR	NR	NR	NR	NR	NR, NSD	Yes
Rollman, 2018[154] (G)(A)	SF-12 MCS	0-100	Better	White	IG1	26	257	77	NR	NR	NR	NR	NR	NR, NSD	Yes
Roy-Byrne, 2010[155] (G)(A)	SF-12 MCS	0-100	Better	All	IG1	26	503	501	31.6 (7.6)	32.1 (10)	12.3 (31.7)	7.9 (11.2)	4.4 (1.5 to 7.4)	<0.001	No
Roy-Byrne, 2010[155] (G)(A)	SF-12 MCS	0-100	Better	All	IG1	52	503	501	31.6 (7.6)	32.1 (10)	14 (40.2)	8.2 (11.6)	5.8 (2.1 to 9.4)	<0.001	No
Roy-Byrne, 2010[155] (G)(A)	SF-12 MCS	0-100	Better	All	IG1	78	503	501	31.6 (7.6)	32.1 (10)	14 (31.5)	9.7 (11.4)	4.3 (1.4 to 7.2)	<0.001	No
Stanley, 2009[158] (O)(A)	SF-12 MCS	0-100	Better	All	IG1	13	65	50	42.4 (10)	41.7 (9.5)	7.2 (9.5)	3.6 (9.5)	3.6 (0.1 to 7.1)	0.008	Yes
Stanley, 2009[158] (O)(A)	SF-12 MCS	0-100	Better	All	IG1	26	53	42	42.4 (10)	41.7 (9.5)	8.8 (9.3)	5.7 (10)	3.1 (-0.8 to 7)	0.52	Yes
Stanley, 2009[158] (O)(A)	SF-12 MCS	0-100	Better	All	IG1	39	54	42	42.4 (10)	41.7 (9.5)	6 (9.7)	6.4 (9.9)	-0.4 (-4.3 to 3.5)	0.52	Yes
Stanley, 2009[158] (O)(A)	SF-12 MCS	0-100	Better	All	IG1	52	51	41	42.4 (10)	41.7 (9.5)	7.8 (9.2)	5.8 (9.9)	2 (-1.9 to 5.9)	0.52	Yes
Stanley, 2009[158] (O)(A)	SF-12 MCS	0-100	Better	All	IG1	61	52	42	42.4 (10)	41.7 (9.5)	7.9 (9.3)	5.3 (10.1)	2.6 (-1.3 to 6.5)	0.52	Yes
Stanley, 2014[159] (O)(A)	SF-12 MCS	0-100	Better	All	IG1	26	60	68	43.3 (10.4)	41.3 (9.9)	6.5 (10.3)	1.7 (10)	4.9 (1.3 to 8.4)	<0.001	Yes

Appendix F Table 13. Quality of Life Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Roy-Byrne, 2010[155] (G)(A)	SF-12 PCS	0-100	Better	All	IG1	26	503	501	49 (9.7)	49.3 (11.4)	-1.2 (13.2)	-2.1 (11.6)	0.9 (-0.7 to 2.4)	0.90	No
Roy-Byrne, 2010[155] (G)(A)	SF-12 PCS	0-100	Better	All	IG1	52	503	501	49 (9.7)	49.3 (11.4)	-1.3 (10.7)	-1.5 (11.7)	0.2 (-1.2 to 1.6)	0.90	No
Roy-Byrne, 2010[155] (G)(A)	SF-12 PCS	0-100	Better	All	IG1	78	503	501	49 (9.7)	49.3 (11.4)	-0.8 (14.7)	-2 (11.7)	1.2 (-0.5 to 2.8)	0.90	No
Stanley, 2009[158] (O)(A)	SF-12 PCS	0-100	Better	All	IG1	13	65	50	44 (8.5)	44.3 (8.2)	-2.4 (8.2)	-2.5 (9)	0.1 (-3.1 to 3.3)	0.87	Yes
Stanley, 2009[158] (O)(A)	SF-12 PCS	0-100	Better	All	IG1	26	53	42	44 (8.5)	44.3 (8.2)	-1.6 (8.1)	-3.8 (9.4)	2.2 (-1.3 to 5.7)	0.9	Yes
Stanley, 2009[158] (O)(A)	SF-12 PCS	0-100	Better	All	IG1	39	54	42	44 (8.5)	44.3 (8.2)	-1.3 (8.1)	-1.7 (8.4)	0.4 (-2.9 to 3.7)	0.9	Yes
Stanley, 2009[158] (O)(A)	SF-12 PCS	0-100	Better	All	IG1	52	51	41	44 (8.5)	44.3 (8.2)	-2.5 (7.8)	-2.6 (8.3)	0.1 (-3.2 to 3.4)	0.9	Yes
Stanley, 2009[158] (O)(A)	SF-12 PCS	0-100	Better	All	IG1	61	52	42	44 (8.5)	44.3 (8.2)	-1.9 (7.9)	-2.5 (8.1)	0.6 (-2.6 to 3.8)	0.9	Yes
Stanley, 2014[159] (O)(A)	SF-12 PCS	0-100	Better	All	IG1	26	60	68	41.1 (12.3)	40.9 (11.2)	0.5 (12.1)	0.1 (11.6)	0.5 (-3.6 to 4.6)	NR	NR
Lam, 2010[148] (O)(A or D)	SF-36 MCS	0-100	Better	All	IG1	6	149	150	49.2 (12.3)	51.7 (12.9)	2.6 (11.2)	0.6 (11.7)	-0.5 (-2.4 to 1.4)	0.592	Yes
Lam, 2010[148] (O)(A or D)	SF-36 MCS	0-100	Better	All	IG1	12	149	150	49.2 (12.3)	51.7 (12.9)	1.9 (11.8)	0.3 (11.7)	-0.5 (-2.4 to 1.4)	0.592	Yes

Appendix F Table 13. Quality of Life Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Lam, 2010[148] (O)(A or D)	SF-36 MCS	0-100	Better	All	IG1	26	149	150	49.2 (12.3)	51.7 (12.9)	-0.5 (13)	1.2 (12)	-0.5 (-2.4 to 1.2)	0.592	Yes
Lam, 2010[148] (O)(A or D)	SF-36 MCS	0-100	Better	All	IG1	52	149	150	49.2 (12.3)	51.7 (12.9)	0.7 (12.5)	1.1 (11.1)	-0.5 (-2.4 to 1.4)	0.592	Yes
Schreuders, 2007[156] (G)(A or D)	SF-36 MCS	0-100	Better	All	IG1	13	61	69	38.1 (10.3)	37.8 (11.1)	3.7 (10.6)	2.5 (11.8)	1.2 (-2.7 to 5.1)	0.391	Yes
Lam, 2010[148] (O)(A or D)	SF-36 PCS	0-100	Better	All	IG1	6	149	150	36.8 (13.6)	37.1 (13.2)	0.7 (10.6)	2.2 (9.4)	-1.5 (-3.2 to 0.3)	0.103	Yes
Lam, 2010[148] (O)(A or D)	SF-36 PCS	0-100	Better	All	IG1	12	149	150	36.8 (13.6)	37.1 (13.2)	-0.1 (11.6)	3.1 (9.9)	-1.5 (-3.2 to 0.3)	0.103	Yes
Lam, 2010[148] (O)(A or D)	SF-36 PCS	0-100	Better	All	IG1	26	149	150	36.8 (13.6)	37.1 (13.2)	-0.5 (10.6)	1.1 (11)	-1.5 (-3.2 to 0.3)	0.103	Yes
Lam, 2010[148] (O)(A or D)	SF-36 PCS	0-100	Better	All	IG1	52	149	150	36.8 (13.6)	37.1 (13.2)	-0.5 (10.2)	0.8 (11)	-1.5 (-3.2 to 0.3)	0.103	Yes
Schreuders, 2007[156] (G)(A or D)	SF-36 PCS	0-100	Better	All	IG1	13	61	69	46.5 (1.7)	41.2 (11.4)	2.8 (10.6)	2.3 (11.7)	0.6 (-3.3 to 4.4)	0.136	Yes

*(G)-General adult population; (O)-Older adult population; (P) Perinatal population; (A) Study required anxiety; (A or D) Anxiety or Depression allowed.

Abbreviations: Adj = Adjusted; BL = baseline; CG = control group; Chg = change; CI = confidence interval; DAS = disability assessment score; Diff = difference; EQ–5D = EuroQol – 5D; FUP = followup; GAD = Generalized Anxiety Disorder assessment; IG = intervention group; MCS = Mental Component Score; NOS = not otherwise specified; NR = not reported; NSD = no significant difference; PBQ = Postpartum Bonding Questionnaire; PCS = physical component score; PHQ = Patient Health Questionnaire; QOLI = Quality of Life Inventory; SD = standard deviation; SF-12 = Short Form – 12-item Health Questionnaire.

Appendix F Table 14. Functioning Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Kendrick, 2005[146] (G)(A or D)	SAS	NR	Worse	All	IG1	8	90	78	NR	NR	FU=2.5 (0.4)	FU=2.5 (0.5)	0 (-0.1 to 0.1)	0.962	Yes
Kendrick, 2005[146] (G)(A or D)	SAS	NR	Worse	All	IG1	26	90	78	NR	NR	FU=2.4 (0.4)	FU=2.3 (0.4)	0.1 (0 to 0.3)	0.137	Yes
Kendrick, 2005[146] (G)(A or D)	SAS	NR	Worse	All	IG2	8	79	78	NR	NR	FU=2.5 (0.4)	FU=2.5 (0.5)	0 (-0.2 to 0.1)	0.784	Yes
Kendrick, 2005[146] (G)(A or D)	SAS	NR	Worse	All	IG2	26	79	78	NR	NR	FU=2.3 (0.4)	FU=2.3 (0.4)	0 (-0.2 to 0.1)	0.659	Yes
King, 2000[147] (G)(A or D)	SAS	1-5	Worse	All	IG1	17	49	54	2.6 (0.5)	2.5 (0.6)	-0.4 (0.5)	-0.3 (0.6)	-0.1 (-0.3 to 0.1)	NR	NR
King, 2000[147] (G)(A or D)	SAS	1-5	Worse	All	IG1	52	45	54	2.6 (0.5)	2.5 (0.6)	-0.7 (0.5)	-0.6 (0.6)	-0.1 (-0.3 to 0.1)	NR	NR
King, 2000[147] (G)(A or D)	SAS	1-5	Worse	All	IG2	17	61	54	2.5 (0.4)	2.5 (0.6)	-0.3 (0.4)	-0.3 (0.6)	0 (-0.2 to 0.2)	NR	NR
King, 2000[147] (G)(A or D)	SAS	1-5	Worse	All	IG2	52	55	54	2.5 (0.4)	2.5 (0.6)	-0.4 (0.5)	-0.6 (0.6)	0.2 (0 to 0.4)	NR	NR
Roy-Byrne, 2010[155] (G)(A)	SDS	0-30	Worse	All	IG1	26	503	501	16.8 (5.1)	17.1 (7.3)	-7.6 (5.5)	-5.5 (7.9)	-2.1 (-3 to -1.3)	<0.001	No
Roy-Byrne, 2010[155] (G)(A)	SDS	0-30	Worse	All	IG1	52	503	501	16.8 (5.1)	17.1 (7.3)	-8.5 (9.8)	-5.5 (8)	-3.1 (-4.2 to -2)	<0.001	No
Roy-Byrne, 2010[155] (G)(A)	SDS	0-30	Worse	All	IG1	78	503	501	16.8 (5.1)	17.1 (7.3)	-8.4 (5.5)	-6.3 (8.1)	-2.1 (-3 to -1.3)	<0.001	No
Proudfoot, 2004[153] (G)(A or D)	WSAS	0-40	Worse	All	IG1	8	105	103	18.4 (9.2)	19.1 (8.3)	-7.2 (8.5)	-4.5 (8.4)	-2.7 (-5 to -0.4)	0.88	Yes
Proudfoot, 2004[153] (G)(A	WSAS	0-40	Worse	All	IG1	13	99	86	18.4 (9.2)	19.1 (8.3)	-7.9 (8.9)	-5.1 (9)	-2.8 (-5.4 to	0.88	Yes

Appendix F Table 14. Functioning Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
or D)													-0.2)		
Proudfoot, 2004[153] (G)(A or D)	WSAS	0-40	Worse	All	IG1	21	95	85	18.4 (9.2)	19.1 (8.3)	-9.3 (8.5)	-7.6 (8.4)	-1.7 (-4.2 to 0.7)	0.88	Yes
Proudfoot, 2004[153] (G)(A or D)	WSAS	0-40	Worse	All	IG1	34	103	94	18.4 (9.2)	19.1 (8.3)	-10.5 (8.6)	-7.3 (9.3)	-3.2 (-5.7 to -0.7)	0.88	Yes

*(G)-General adult population; (O)-Older adult population; (P) Perinatal population; (A) Study required anxiety; (A or D) Anxiety or Depression allowed.

Abbreviations: Adj = adjusted; BL = baseline; CG = control group; Chg = change; CI = confidence interval; Diff = difference; FUP = followup; IG = intervention group; NR = not reported; SD = standard deviation; SAS = Zung Self-Rating Anxiety Scale; SDS = Sheehan Disability Scale; WSAS = Work and Social Adjustment Scale.

Appendix F Table 15. Other Health Outcome Results for Primary Research Studies of Psychological Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Pop)*	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Burger, 2020[140] (Pr)(A or D)	APGAR	1-10	Better	All	IG1	p0	121	120	NR	NR	FU=9.5 (1)	FU=9.5 (1)	-0.1 (-0.3 to 0.2)	0.680	Yes
Burger, 2020[140] (Pr)(A or D)	Birth weight, g	NA	NA	All	IG1	p0	123	120	NR	NR	FU=3413 (647)	FU=3457 (561)	-53.5 (-196.3 to 89.2)	0.462	Yes
Burger, 2020[140] (Pr)(A or D)	Gestational age	NA	NA	All	IG1	p0	122	121	NR	NR	FU=38.5 (2.3)	FU=38.8 (1.8)	-0.3 (-0.8 to 0.2)	0.217	Yes
Rollman, 2018[154] (G)(A)	Emergency room visits	NA	NA	All	IG1	26	301	101	NR	NR	NR	NR	NR	NR, NSD	NR
Rollman, 2018[154] (G)(A)	Emergency room visits	NA	NA	All	IG2	26	302	101	NR	NR	NR	NR	NR	NR, NSD	NR
Rollman, 2018[154] (G)(A)	Hospitalizations	NA	NA	All	IG1	26	301	101	NR	NR	NR	NR	NR	NR, NSD	NR
Rollman, 2018[154] (G)(A)	Hospitalizations	NA	NA	All	IG2	26	302	101	NR	NR	NR	NR	NR	NR, NSD	NR

*(G)-General adult population; (O)-Older adult population; (P) Perinatal population; (A) Study required anxiety; (A or D) Anxiety or Depression allowed.

Abbreviations: Adj = adjusted; BL = baseline; CG = control group; Chg = change; CI = confidence interval; Diff = difference; IG = intervention group; FU = followup; NA = not applicable; NR = not reported; NSD = no significant difference; SD = standard deviation.

Appendix F Table 16. Results for Other Outcomes From ESRs of Psychological Treatment of Anxiety Compared to Controls (KQ4)

Author, Year	Population	Intervention	Control	Outcome	Followup	k	N analyzed	SMD (95% CI)	I^2 (%)
Hofmann, 2014[166]	All participants	CBT	Any	QoL	Post-tx	21	NR	-0.56 (-0.80 to -0.32)	NR
Cuijpers, 2016[164]	GAD	CBT	Any	Depression sx	Post-tx	21	NR	-0.68 (-0.82 to -0.53)	12
	GAD (Low RoB only)	CBT	Any	Depression sx	Post-tx	6	NR	-0.53 (-0.76 to -0.31)	25
	SAnD	CBT	Any	Depression sx	Post-tx	19	NR	-0.79 (-1.04 to -0.53)	71
	SAnD (Low RoB only)	CBT	Any	Depression sx	Post-tx	4	NR	-0.59 (-0.98 to -0.20)	65
	PD	CBT	Any	Depression sx	Post-tx	28	NR	-0.47 (-0.73 to -0.21)	73
	PD (Low RoB only)	CBT	Any	Depression sx	Post-tx	2	NR	-0.85 (-1.40 to -0.30)	45

Abbreviations: CBT = cognitive behavioral therapy; GAD = generalized anxiety disorder; NR = not reported; PD = panic disorder; QoL = quality of life; RoB = risk of bias; SAnD = social anxiety disorder; SMD = standardized mean difference Sx =symptoms; tx = treatment.

Appendix F Table 17. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Pharmacologic Treatment of Anxiety (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Balasubramaniam, 2019[130]	Treatment studies, comprised exclusively of participants with a mean or median age of ≥60 years and focused on ≥1 anxiety disorders as the outcome of interest.	Tx studies that included antidepressants as the primary intervention and had a blinded RCT design.	NR	NR	NR
Bighelli, 2018[11]	Participants age ≥18 years with a primary diagnosis of panic disorder, with or without agoraphobia, diagnosed according to any of the following criteria: Feighner criteria, Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV or ICD-10.	Any trial comparing antidepressants as monotherapy with placebo in the treatment of panic disorder, with or without agoraphobia; included only acute treatment studies treating participants for less than 6 months; studies in which irregular (i.e., not daily) use of benzodiazepines took place.	Placebo	NR	NR
Breilmann, 2019[168]	People age ≥18 years and with diagnosis of panic disorder, with or without agoraphobia, diagnosed according to any of the following criteria: Feighner criteria, Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV, DSM-5, or ICD-10; and included participants with comorbid mental disorders.	Any trial comparing a benzodiazapine as monotherapy (alprazolam, bretazenil, bromazepam, chlordiazepoxide, cinolazepam, clonazepam, cloxazolam, clorazepate, diazepam, estazolam, fludiazepam, flunitrazepam, flurazepam, flutoprazepam, halazepam, ketazolam, loprazolam, lorazepam, medazepam, nimatazepam, nitrazepam, nodazepam, oxazepam, phenazepam, pinazepam, prazepam, premazepam, quazepam, temazepam, tetrazepam, and triazolam) with placebo in the	Placebo	Included all types: inpatient, outpatient, and primary care	Primary outcomes: Rate of response (i.e., substantial improvement from baseline as defined by the original investigators); and total number of dropouts for any reason as a proxy measure of treatment acceptability

Appendix F Table 17. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Pharmacologic Treatment of Anxiety (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
		treatment of panic disorder, with or without agoraphobia; included acute treatment studies treating participants for less than 6 months.			
Chen, 2019[169]	Trials of adult patients with a diagnosis of GAD (allowed for all comorbidities).	Eligible interventions for GAD were oral drugs, psychological interventions, and self-help interventions; all antidepressants—TCAs, SSRIs, SNRIs, norepinephrine–dopamine reuptake inhibitors (NDRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), agomelatine, vilazodone, and vortioxetine. The other pharmacological interventions were included mainly based on guidelines and evidence, but they were not necessarily licensed for GAD.	NR	NR	NR
Gupta, 2020[170]	Study population of age ≥55 years with anxiety disorder.	Studies in which at least 1 of the tx arms received benzodiazepines; benzodiazepine efficacy studies to tx anxiety.	NR	NR	NR
Imai, 2014[12]	Adults (age ≥18 years) with a primary diagnosis of panic disorder with or without agoraphobia and diagnosed according to any of the following criteria: Feighner criteria, Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV, or ICD-10; included participants with comorbid mental	Monotherapy with azapirones (buspirone, gepirone,tandospirone, ipsapirone or lesopitron); acute treatment for ≤6 months.	Placebo	All trials were conducted in the outpatient setting; in the US.	Frequency of panic attacks was used in all the studies.

Appendix F Table 17. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Pharmacologic Treatment of Anxiety (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
	disorders				
Roest, 2015[171]	NR	Second-generation antidepressants for the treatment of GAD, PD, SAD, PTSD, and OCD. Nine drugs approved by the FDA for these indications.	Placebo	NR	Reporting bias was examined and classified as study publication bias, outcome reporting bias, or spin.
Slee, 2019[10]	Adult outpatients; generalized anxiety disorder diagnosed by DSM-IV, DSM IV-TR, DSM V, ICD-10, or CCMD-3; inclusion of at least 10 participants in each group.	Comparison of at least two commercially available pharmacological options or placebo.	Placebo and active control trials.	NR	Studies reporting change from baseline on a scale intended to measure anxiety.
Viswanathan, 2021[107]	For tx: Studies in women who are pregnant or postpartum with new or preexisting diagnosis of anxiety, depression, bipolar disorder, or schizophrenia. For tx harms: Reproductive-aged women (age 15-44 years during preconception [≤12 weeks before pregnancy], pregnancy, and postpartum [through 1 year]) with any mental health disorder (new or preexisting).	All US FDA-approved drugs for mental health disorders and off-label drugs used for mental health disorders were eligible.	Placebo or no tx, or other pharmacologic interventions.	NR	NR

Appendix F Table 17. Detailed Inclusion and Exclusion Criteria of Existing Systematic Reviews Addressing Benefits of Pharmacologic Treatment of Anxiety (KQ4)

Author, Year	Population Criteria	Intervention Criteria	Control Criteria	Setting Criteria	Outcome Notes
Williams, 2017[13]	Adult participants diagnosed with SAnD irrespective of diagnostic criteria and measure, duration and severity of SAnD symptoms, age, and sex.	Any medication administered to treat SAnD: 5HT1A partial agonists (e.g., buspirone), anticonvulsants/gamma-amino butyric acids (GABAs, e.g., gabapentin and pregabalin), the anticonvulsant levetiracetam, antipsychotics (e.g., olanzapine), benzodiazepines (e.g., clonazepam and bromazepam), beta-blockers (e.g., atenolol), mono-amine oxidase inhibitors (MAOIs, e.g., brofaromine and moclobemide), noradrenaline reuptake inhibitors (NARIs, e.g., atomoxetine and mirtazepine), noradrenergic and specific serotonergic antidepressants (NaSSAs, e.g., mirtazepine), reversible inhibitors of monoamine oxidase A (RIMAs, e.g., phenelzine), serotonin antagonist and reuptake inhibitors (SARIs, e.g., nefazodone), serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine), selective serotonin reuptake inhibitors (SSRIs, e.g. paroxetine, fluvoxamine, sertraline, fluoxetine and citalopram), other medications (e.g. GW876008, GR205171 and LY686017).	An active or non-active placebo	No restrictions	NR

Abbreviations: CCMD-3 = Chinese Classification of Mental Disorders - Version 3; DSM = Diagnostic and Statistical Manual; FDA = Food and Drug Administration; GAD = generalized anxiety disorder; ICD = International Classification of Diseases; NR = not reported; OCD = obsessive compulsive disorder; PD = panic disorder; PTSD = post-traumatic stress disorder; RCT = randomized, controlled trials; SAD = social anxiety disorder; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressants; Tx = treatment; US = United States.

Appendix F Table 18. Anxiety Outcome Results for Primary Research Studies of Pharmacologic Treatment of Anxiety in Primary Care Populations (KQ4)

Author, Year (Agent)	Analyzed	Outcome	Measure	FUP, wks	IG n	CG n	IG mean chg (SD) or n/N (%)	CG mean chg (SD) or n/N (%)	Effect type	Between-group difference, p-value
Lenox-Smith, 2003[172] (Venl)	All	Anxiety remission	Recovery from anxiety	24	107	97	14/107 (13.1)	8/97 (8.2)	calc OR	1.67 (0.67 to 4.19), 0.11
	All	Anxiety response	Response to treatment	24	107	97	56/107 (52.5)	47/97 (48.7)	calc OR	1.17 (0.67 to 2.02), 0.61
	All	Anxiety symptoms	HAM-A	24	122	122	NR	NR	MeanDiff	-2.10 (0.00 to -4.20), 0.05
	All	Depression symptoms	MADRS	8	122	122	NR	NR	MeanDiff	-1.50 (-3.10 to 0.10), 0.072
	All	Depression symptoms	MADRS	24	122	122	NR	NR	MeanDiff	-1.80 (-3.70 to 0.00), 0.053
	All	Global mental health symptoms	HADS	24	122	122	NR	NR	MeanDiff	-2.60 (-4.70 to -0.60), 0.013
	All	Global mental health symptoms	HADS	8	122	122	NR	NR	MeanDiff	-2.70 (-4.50 to -0.80), 0.005
	All	Quality of Life	SF36 - Mental health	24	122	122	FUP= 58.1 (22.3)	FUP= 48.7 (21.2)	LSMChange	8.30 (3.30 to 13.40), 0.001
	All	Quality of Life	SF36 - Mental health	8	122	122	FUP= 56.7 (21.7)	FUP= 46 (20.6)	LSMChange	9.50 (4.70 to 14.20), <0.001
Lenze, 2009[173] (Escit)	All	Anxiety response	Response to treatment	12	85	92	51/85 (60.0)	41/92 (45.0)	calc OR	1.87 (1.03 to 3.39), 0.048
	All	Anxiety symptoms	HAM-A	12	84	91	NR	NR	CohensD	-0.23 (-0.49 to 0.02), 0.06
	All	Global mental health symptoms	CGI-I	12	84	91	NR	NR	CohensD	-0.93 (-0.50 to -1.36), <0.001

Appendix F Table 18. Anxiety Outcome Results for Primary Research Studies of Pharmacologic Treatment of Anxiety in Primary Care Populations (KQ4)

Abbreviations: calcOR = calculated odds ratio; CG = control group; CGI-I = Clinical Global Impression – Global Improvement; chg = change; FUP = followup; HADS = Hospital Anxiety and Depression Scale; HAM–A = Hamilton Rating Scale for Anxiety; IG = intervention group; LSMchange = least squares mean change; MADRS = Montgomery–Asberg Depression Rating Scale; MeanDiff = mean difference; NR = not reported; SD = standard deviation; SF = short form.

Appendix F Table 19. Results for Anxiety Symptoms Severity From ESRs of Pharmacologic Treatment of Anxiety Compared to Controls (KQ4)

Author, Year	Specific d/o	Intervention	Population	Control	Outcome	Followup	k	N analyzed	Effect	ES (95% CI)	I^2 (%)
Chen, 2019[169]	GAD	SSRI	All participants	Placebo	Main anxiety outcome	Post-tx	23	2142	SMD	-0.66 (-0.90 to -0.43)	NR
	GAD	SNRI	All participants	Placebo	Main anxiety outcome	Post-tx	13	1666	SMD	-0.54 (-0.79 to -0.30)	NR
	GAD	Serotonin modulator	All participants	Placebo	Main anxiety outcome	Post-tx	8	1801	SMD	-0.23 (-0.53 to 0.06)	NR
	GAD	Bupropion	All participants	Placebo	Main anxiety outcome	Post-tx	1	11	SMD	-1.84 (-3.05 to -0.62)	NR
	GAD	Mirtazapine	All participants	Placebo	Main anxiety outcome	Post-tx	2	69	SMD	-0.91 (-1.62 to -0.20)	NR
	GAD	Buspirone	All participants	Placebo	Main anxiety outcome	Post-tx	7	221	SMD	-0.58 (-0.98 to -0.17)	NR
	GAD	Benzodiazepine	All participants	Placebo	Main anxiety outcome	Post-tx	22	920	SMD	-0.40 (-0.65 to -0.15)	NR
	GAD	Agomelatine	All participants	Placebo	Main anxiety outcome	Post-tx	3	470	SMD	-0.68 (-1.15 to -0.21)	NR
Bighelli, 2018[11]	PD	Antidepressants	All participants (Endpoint)	Placebo	Anxiety Sx	8-28	17	3168	SMD	-0.46 (-0.63 to -0.29)	71
	PD	Antidepressants	All participants (Mean change)	Placebo	Anxiety Sx	8-28	12	2477	SMD	-0.33 (-0.47 to -0.20)	57
	PD	Antidepressants	All participants (Endpoint)	Placebo	Panic symptoms	8-28	15	3699	SMD	-0.44 (-0.58 to -0.30)	68
	PD	Antidepressants	All	Placebo	Panic	8-28	10	2010	SMD	-0.53	73

Appendix F Table 19. Results for Anxiety Symptoms Severity From ESRs of Pharmacologic Treatment of Anxiety Compared to Controls (KQ4)

Author, Year	Specific d/o	Intervention	Population	Control	Outcome	Followup	k	N analyzed	Effect	ES (95% CI)	I^2 (%)
			participants (Mean change)		symptoms					(-0.72 to -0.33)	
	PD	Antidepressants	All participants (Mean change)	Placebo	Panic attacks	8-28	8	2579	SMD	-0.43 (-0.72 to -0.14)	91
	PD	Antidepressants	All participants (Endpoint)	Placebo	Panic attacks	8-28	16	1671	SMD	-0.43 (-0.66 to -0.20)	78
	PD	Antidepressants	All participants (Mean change)	Placebo	Agoraphobia	8-28	7	1792	SMD	-0.68 (-1.19 to -0.17)	96
	PD	Antidepressants	All participants (Endpoint)	Placebo	Agoraphobia	8-28	13	2987	SMD	-0.69 (-0.99 to -0.39)	91
Imai, 2014[12]	PD	Buspirone	All participants	Placebo	Agoraphobia	8	1	52	SMD	-0.01 (-0.56 to 0.53)	NA
Breilmann, 2019[168]	PD	Benzodiazepine	All participants (Mean change)	Placebo	Panic symptoms	3-15	4	719	SMD	-0.50 (-0.87 to -0.13)	79.61
	PD	Benzodiazepine	All participants (Endpoint)	Placebo	Panic symptoms	3-15	7	1489	SMD	-0.92 (-1.22 to -0.61)	77.4
	PD	Benzodiazepine	All participants	Placebo	Agoraphobia	3-15	13	2371	SMD	-0.35 (-0.50 to -0.20)	58.54

Abbreviations: CI = confidence interval; d/o = disorder; ES = effect size; ESR = existing systematic review; GAD = generalized anxiety disorder; NA = not applicable; NR = not reported; PD = panic disorder; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; SMD = standardized mean difference; Sx = symptoms; Tx = treatment.

Appendix F Table 20. Results for Anxiety Remission From ESRs of Pharmacologic Treatment of Anxiety Compared to Controls (KQ4)

Author, Year	Specific d/o	Intervention	Outcome	Population	Control	Followup	k	N analyzed	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Bighelli, 2018[11]	PD	Antidepressants	Failure to remit	All participants	Placebo	8-28	24	6164	1875/3682 (50.9)	1477/2482 (59.5)	RR	0.83 (0.78 to 0.88)	40
Breilmann, 2019[168]	PD	Benzodiazepine	Anxiety remission	All participants	Placebo	3-15	15	2907	1074/1702 (63.1)	487/1205 (40.4)	RR	1.61 (1.38 to 1.88)	61.77

Abbreviations: CG = control group; CI = confidence interval; d/o = disorder; ES = effect size; ESR = existing systematic review; IG = intervention group; PD = panic disorder; RR = relative risk.

Appendix F Table 21. Results for Anxiety Response to Treatment From ESRs of Pharmacologic Treatment of Anxiety Compared to Controls (KQ4)

Author, Year	Specific d/o	Outcome	Intervention	Population	Control	Followup	k	N analyzed	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Bighelli, 2018[11]	PD	Failure to respond	Antidepressants	All participants (Excl industry-funded)	Placebo	8-28	12	1183	335/734 (45.6)	272/449 (60.6)	RR	0.78 (0.66 to 0.92)	62
	PD	Failure to respond	Antidepressants	All participants (Excl high risk of bias)	Placebo	8-28	18	3819	1039/2302 (45.1)	873/1517 (57.5)	RR	0.79 (0.72 to 0.87)	56
	PD	Failure to respond	Antidepressants	All participants	Placebo	8-28	31	6500	1608/4068 (39.5)	1352/2432 (55.6)	RR	0.72 (0.66 to 0.79)	67
Breilmann, 2019[168]	PD	Anxiety response	Benzodiazepine	All participants (Excl high risk of bias)	Placebo	3-15	3	215	83/121 (68.6)	55/94 (58.5)	RR	1.80 (0.67 to 4.84)	62.4
	PD	Anxiety response	Benzodiazepine	All participants	Placebo	3-15	16	2476	999/1536 (65.0)	387/940 (41.2)	RR	1.65 (1.39 to 1.96)	67.01
	PD	Anxiety response	Benzodiazepine	All participants (Excl w comorbidities)	Placebo	3-15	11	1778	694/1110 (62.5)	261/668 (39.1)	RR	1.63 (1.38 to 1.94)	44.74
	PD	Anxiety response	Benzodiazepine	All participants (Excl >20% attrition)	Placebo	3-15	6	640	235/392 (59.9)	95/248 (38.3)	RR	1.78 (1.17 to 2.71)	68.32
Williams, 2017[13]	SAnD	Anxiety response	Pharmacologic	All participants (Trials exclude MDD)	Placebo	16+	34	6765	2002/3881 (47.3)	1003/2884 (27.2)	RR	1.51 (1.35 to 1.70)	66

Appendix F Table 21. Results for Anxiety Response to Treatment From ESRs of Pharmacologic Treatment of Anxiety Compared to Controls (KQ4)

Author, Year	Specific d/o	Outcome	Intervention	Population	Control	Followup	k	N analyzed	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
	SAnD	Anxiety response	Pharmacologic	All participants (Industry-funded)	Placebo	16+	34	6643	2040/3782 (53.8)	957/2861 (31.7)	RR	1.60 (1.44 to 1.77)	59
	SAnD	Anxiety response	Pharmacologic	All participants (Trials include MDD)	Placebo	16+	20	2654	660/1396 (47.3)	342/1258 (27.2)	RR	1.77 (1.44 to 2.18)	70
	SAnD	Anxiety response	Pharmacologic	All participants (Excl Industry funded)	Placebo	16+	16	1780	374/904 (41.4)	223/876 (25.5)	RR	1.99 (1.43 to 2.77)	77
	SAnD	Anxiety response	SSRI	All participants	Placebo	20-24	4	806	308/405 (76.0)	232/401 (57.9)	RR	1.27 (1.07 to 1.51)	60
	SAnD	Anxiety response	SSRI	All participants	Placebo	16+	24	4984	1489/2767 (53.8)	703/2217 (31.7)	RR	1.65 (1.48 to 1.85)	50
	SAnD	Anxiety response	SNRI	All participants	Placebo	16+	4	1173	318/630 (50.5)	203/543 (37.4)	RR	1.30 (0.85 to 1.99)	89
	SAnD	Anxiety response	Mirtazapine	All participants	Placebo	16+	1	60	4/30 (13.3)	4/30 (13.3)	RR	1.0 (0.28 to 3.63)	NA
	SAnD	Anxiety response	Buspirone	All participants	Placebo	16+	1	30	1/15 (6.7)	1/15 (6.7)	RR	1.0 (0.07 to 14.55)	NA
	SAnD	Anxiety response	Benzodiazepine	All participants	Placebo	16+	2	132	54/67 (80.6)	13/65 (20.0)	RR	4.03 (2.45	0

Appendix F Table 21. Results for Anxiety Response to Treatment From ESRs of Pharmacologic Treatment of Anxiety Compared to Controls (KQ4)

Author, Year	Specific d/o	Outcome	Intervention	Population	Control	Followup	k	N analyzed	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
												to 6.65)	

Abbreviations: CG = control group; CI = confidence interval; d/o =disorder; ES = effect size; ESR = existing systematic review; Excl = excluded; IG = intervention group; MDD = major depressive disorder; NA = not applicable; PD = panic disorder; RR = relative risk; SAnD = social anxiety disorder; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Appendix F Table 22. Results for Other Outcomes From ESRs of Pharmacologic Treatment of Anxiety Compared to Controls (KQ4)

Author, Year	Specific d/o	Intervention	Outcome	Population	Control	Followup	k	N analyzed	Effect	ES (95% CI)	I^2 (%)
Bighelli, 2018[11]	PD	Antidepressants	Depression sx	All participants (Endpoint)	Placebo	8-28	12	1794	SMD	-0.41 (-0.57 to -0.25)	43
	PD	Antidepressants	Depression sx	All participants (Mean change)	Placebo	8-28	7	1052	SMD	-0.40 (-0.55 to -0.24)	28
	PD	Antidepressants	Poor QoL	All participants	Placebo	8-28	6	1675	SMD	-0.13 (-0.29 to 0.03)	59
	PD	Antidepressants	Social disability	All participants (Endpoint)	Placebo	8-28	9	1872	SMD	-0.29 (-0.40 to -0.18)	11
	PD	Antidepressants	Social disability	All participants (Mean change)	Placebo	8-28	7	1429	SMD	-0.29 (-0.42 to -0.16)	27
Imai, 2014[12]	PD	Buspirone	HAMD	All participants	Placebo	8	1	52	MD	-1.8 (-5.6 to 2.0)	NA
Breilmann, 2019[168]	PD	Benzodiazepine	Depression sx	All participants (Endpoint)	Placebo	3-15	8	968	SMD	-0.70 (-1.08 to -0.32)	78.05
	PD	Benzodiazepine	Depression sx	All participants (Mean change)	Placebo	3-15	4	441	SMD	-0.22 (-0.48 to 0.04)	39.69
	PD	Benzodiazepine	Social disability	All participants (Endpoint)	Placebo	3-15	4	1146	SMD	-0.53 (-0.65 to -0.42)	0
	PD	Benzodiazepine	Social disability	All participants (Mean change)	Placebo	3-15	2	202	SMD	-0.32 (-0.88 to 0.24)	69.82

Appendix F Table 22. Results for Other Outcomes From ESRs of Pharmacologic Treatment of Anxiety Compared to Controls (KQ4)

Author, Year	Specific d/o	Intervention	Outcome	Population	Control	Followup	k	N analyzed	Effect	ES (95% CI)	I^2 (%)
Williams, 2017[13]	SAnD	SSRI	Depression sx	All participants	Placebo	≤16	6	960	SMD	-0.26 (-0.48 to -0.03)	55
	SAnD	SSRI	Social disability	All participants	Placebo	≤16	5	854	Mean difference	-0.9 (-1.3 to -0.5)	0
	SAnD	SSRI	Family fx disability	All participants	Placebo	≤16	5	854	Mean difference	-0.4 (-0.8 to -0.2)	0
	SAnD	SSRI	Work disability	All participants	Placebo	≤16	5	854	Mean difference	-0.8 (-1.2 to -0.4)	0
	SAnD	Nefazodone	HAMD	All participants	Placebo	≤16	1	102	Mean difference	0.8 (-2.1 to 3.7)	NA
	SAnD	Nefazodone	Social disability	All participants	Placebo	≤16	1	102	Mean difference	-1.0 (-2.0 to -0.03)	NA
	SAnD	Nefazodone	Family fx disability	All participants	Placebo	≤16	1	102	Mean difference	-0.2 (-1.1 to 0.7)	NA
	SAnD	Nefazodone	Work disability	All participants	Placebo	≤16	1	102	Mean difference	-0.9 (-1.9 to 0.1)	NA
	SAnD	Buspirone	HAMD	All participants	Placebo	≤16	1	30	Mean difference	-0.6 (-2.9 to 1.7)	NA
	SAnD	Benzodiazepine	HAMD	All participants	Placebo	≤16	1	75	Mean difference	-1.6 (-4.0 to 0.8)	NA
	SAnD	Benzodiazepine	Social disability	All participants	Placebo	≤16	2	135	Mean difference	-2.3 (-3.8 to -0.8)	93
	SAnD	Benzodiazepine	Family fx disability	All participants	Placebo	≤16	2	135	Mean difference	-2.0 (-4.3 to	93

Appendix F Table 22. Results for Other Outcomes From ESRs of Pharmacologic Treatment of Anxiety Compared to Controls (KQ4)

Author, Year	Specific d/o	Intervention	Outcome	Population	Control	Followup	k	N analyzed	Effect	ES (95% CI)	I^2 (%)
										0.2)	
	SAnD	Benzodiazepine	Work disability	All participants	Placebo	≤16	2	135	Mean difference	-3.6 (-6.4 to -0.8)	93

Abbreviations: CI = confidence interval; d/o = disorder; ES = effect size; ESR = existing systematic review; fx = functioning; HAM-D = Hamilton Rating Scale for Depression; NA = not applicable; PD = panic disorder; QoL = quality of life; SAnD = social anxiety disorder; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitor; sx = symptoms.

Appendix F Table 23. Results From Narrative Syntheses of Pharmacological Treatment of Anxiety (KQ4)

Author, Year	Specific d/o	Intervention	Control	Population	Outcome	Findings
Balasubramaniam, 2019[130]	None	Antidepressants	Any	Older adults	Main anxiety outcome	In 7 placebo-controlled and 1 waitlist-controlled trials limited to older adults, most limited to GAD, antidepressants were associated with reduced anxiety symptoms after 8 to 15 weeks of treatment.
	None	Antidepressants	Any	Older adults	Tolerability	In 5 of 8 trials of escitalopram, citalopram, duloxetine, or venlafaxine compared with a control group, most reported increased side effects with medication; most common side effects were GI-related, fatigue/sedation, and sleep-related.
Roest, 2015[171]	None	2nd-generation antidepressants	Placebo	All participants	Main anxiety outcome	The findings of 41 of the 57 trials (72%) were positive according to the FDA, but 43 of the 45 published article conclusions (96%) were positive (P<.001). Trials that the FDA determined as positive were 5 times more likely to be published in agreement with that determination compared with trials determined as not positive (risk ratio, 5.20 [95% CI, 1.87 to 14.45]; P<.001). We found evidence for study publication bias (P<.001), outcome reporting bias (P=.02), and spin (P=.02). The pooled effect size based on the published literature (Hedges g, 0.38 [95% CI, 0.33 to 0.42]; P<.001) was 15% higher than the effect size based on the FDA data (Hedges g, 0.33 [95% CI, 0.29 to 0.38]; P<.001), but this difference was not statistically significant (β = 0.04; 95% CI, -0.02 to 0.10; P=.18).
Gupta, 2020[170]	None	Benzodiazepine	Placebo	Older adults	Main anxiety outcome	In 3 of 4 placebo-controlled trials limited to older adults with GAD, PD, or anxiety disorders NOS, benzodiazepines were associated with decreased anxiety during

Appendix F Table 23. Results From Narrative Syntheses of Pharmacological Treatment of Anxiety (KQ4)

Author, Year	Specific d/o	Intervention	Control	Population	Outcome	Findings
						the 4 to 8-week study period (p<.05).
Viswanathan, 2021[107]	None	Benzodiazepine	Placebo	Perinatal	Main anxiety outcome	No studies were found of pharmacologic treatment (benzodiazepines or other anxiolytics) for anxiety among perinatal women.
Gupta, 2020[170]	None	Benzodiazepine	Placebo	Older adults	Tolerability	Limited tolerability data showed mild adverse effects such as drowsiness, faintness, and light-headedness were more common with benzodiazepines than placebo.
Bighelli, 2018[11]	PD	Antidepressants	Placebo	All participants	Depression sx	TCA: -0.54, SSRI: -0.27; both stat sig
	PD	Antidepressants	Placebo	All participants	Depression sx	TCA: -0.58, SSRI: -0.36; both stat sig
	PD	Antidepressants	Placebo	All participants	Anxiety Sx	Range of SMDs for TCA, SSRI, SNRI: -0.62 to -0.26; SSRI & SNRI stat sig
	PD	Antidepressants	Placebo	All participants	Anxiety Sx	TCA: -0.35, SSRI: -0.42 (both p<.05)
	PD	Antidepressants	Placebo	All participants	Panic symptoms	Range of SMDs for TCA, SSRI, SNRI: -0.50 to -0.28; all stat sig
	PD	Antidepressants	Placebo	All participants	Panic symptoms	Range of SMDs for TCA, SSRI, SNRI: -2.09 to -0.41; all stat sig
	PD	Antidepressants	Placebo	All participants	Panic attacks	Range of SMDs for TCA, SSRI, SNRI: -0.87 to -0.08; SSRI & SNRI stat sig
	PD	Antidepressants	Placebo	All participants	Panic attacks	TCA: -0.83, SSRI: -0.17 (both p<.05)
	PD	Antidepressants	Placebo	All participants	Agoraphobia	TCA: -0.59 (NS), SSRI: -0.50 (p<.05)
	PD	Antidepressants	Placebo	All participants	Agoraphobia	Range of SMDs for TCA, SSRI, SNRI: -1.22 to -0.33; TCA & SNRI stat sig
	PD	Antidepressants	Placebo	All participants	Failure to respond	Range of effects for TCA, SSRI, SNRI: 0.61 to 0.75; all stat sig
	PD	Antidepressants	Placebo	All participants	Failure to remit	Range of effects for TCA, SSRI, SNRI: 0.82 to 0.84; all stat sig

Appendix F Table 23. Results From Narrative Syntheses of Pharmacological Treatment of Anxiety (KQ4)

Author, Year	Specific d/o	Intervention	Control	Population	Outcome	Findings
	PD	Antidepressants	Placebo	All participants	QoL	SSRI: -0.28 (p<.05), SNRI: 0.03 (NS)
	PD	Antidepressants	Placebo	All participants	Social Fx	Range of SMDs for TCA, SSRI, SNRI: -0.40 to -0.10; TCA & SSRI stat sig
	PD	Antidepressants	Placebo	All participants	Social Fx	Range of SMDs for TCA, SSRI, SNRI: -0.43 to -0.15; TCA & SSRI stat sig
	PD	Antidepressants	Placebo	All participants	Any adverse events	Range of effects for TCA, SSRI, SNRI: 1.09 to 1.22; all stat sig
	PD	Antidepressants	Placebo	All participants	Dropouts due to AE	Range of effects for TCA, SSRI, SNRI: 1.45 to 1.97; all stat sig
	PD	Antidepressants	Placebo	All participants	Dropouts for any reason	Range of effects for TCA, SSRI, SNRI: 0.74 to 0.99; only TCA stat sig
	PD	Antidepressants	Placebo	All participants	All outcomes included in ESR	Antidepressants other than TCA, SSRI, and SNRI had only 0-1 studies and total n ≤75 for almost all outcomes.
Williams, 2017[13]	SAnD	SSRI	Placebo	All participants	Anxiety response	No difference in ES between studies that did and did not include people with MDD
	SAnD	SSRI	Placebo	All participants	Anxiety response	No difference in ES between industry funded and non-industry funded

Abbreviations: AE = adverse effect; CI = confidence interval; d/o = disorder; ES = effect size; ESR = existing systematic review; FDA = Food and Drug Administration; Fx = functioning; GAD = generalized anxiety disorder; GI = gastrointestinal; MDD = major depressive disorder; NOS = not otherwise specified; NS = nonsignificant; PD = panic disorder; QoL = quality of life; SAnD = social anxiety disorder; SMD = standardized mean difference; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; stat sig = statistically significant; sx = symptoms; TCA = tricyclic antidepressants.

Appendix F Table 24. Results for Adverse Events From Primary Studies of Pharmacologic Treatment of Anxiety Compared to Placebo (KQ5)

Author, Year (Pop)	Intervention	Outcome	Group	FUP, wks	OR (95% CI)	IG n/N (%)	CG n/N (%)	p	Non-serious
Lader, 1998[174] (G)	Buspirone	Adverse events (any)	All participants	4	1.53 (0.79 to 2.96)	31/82 (38.0)	23/81 (28.0)	NR	NR
	Buspirone	Non-serious AEs >5%	All participants	4	See text	NR	NR	NR	Headache and Migraine: IG: 6.1%, CG: 1.2% Dizziness: IG: 6.1%, CG: 2.5% (p-values NR)
	Buspirone	Serious Adverse Events (any)	All participants	4	0.99 (0.02 to 50.38)	0/82 (0.0)	0/81 (0.0)	NR	NR
Lenze, 2009[173] (O)	Escitalopram	Adverse events (any)	All participants	12	1.82 (0.94 to 3.51)	65/85 (76.5)	59/92 (64.0)	0.10	NR
	Escitalopram	Non-serious AEs >5%	All participants	12	See text	NR/85 (NR)	NR/92 (NR)	NR	Fatigue or somnolence (p≤.001, 41% vs 11%) GI upset (p=.73) Headache (p=.15) Sleep disturbance (p=.004, 14% vs 2%) Sweating (p=.11) Sexual (p=.07) Urinary symptoms (p=.002, 9% vs 0%) Increased anxiety or depression (p=.80) Light-headedness (p=.99) Tremor (p=.09) Aches (p=.05, 6% vs 15%) Rash or pruritus (p=.99)
	Escitalopram	Serious Adverse Events (any)	All participants	12	1.08 (0.02 to 55.13)	0/85 (0.0)	0/92 (0.0)	NR	NR
	Escitalopram	Withdrawal due to AE	All participants	12	0.8 (0.17 to 3.71)	3/85 (3.5)	4/92 (4.3)	0.99	NR

Appendix F Table 24. Results for Adverse Events From Primary Studies of Pharmacologic Treatment of Anxiety Compared to Placebo (KQ5)

Author, Year (Pop)	Intervention	Outcome	Group	FUP, wks	OR (95% CI)	IG n/N (%)	CG n/N (%)	p	Non-serious
Lenox-Smith, 2003[172] (G)	Venlafaxine XL	Adverse events (any)	All participants	24	1.22 (0.51 to 2.94)	112/122 (92.0)	110/122 (90.0)	NR	NR
	Venlafaxine XL	Serious Adverse Events (any)	All participants	24	0.79 (0.21 to 3.03)	4/122 (3.3)	5/122 (4.1)	NR	NR

Abbreviations: AE = adverse event; CG = control group; CI = confidence interval; FUP = followup; GI = gastrointestinal; IG = intervention group; NR = not reported; OR = odds ratio.

Appendix F Table 25. Results for Adverse Events From ESRs of Pharmacologic Treatment of Anxiety Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome	Specific d/o	Population	Control	Followup	k	N analyzed	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Bighelli, 2018[11]	Antidepressants	Any adverse events	PD	All participants	Placebo	8-28	16	4246	2077/2708 (76.7)	1036/1538 (67.4)	RR	1.11 (1.07 to 1.15)	0.0
	Benzodiazepine	Any adverse events	PD	All participants	Placebo	3-15	4	658	286/336 (85.1)	227/322 (70.5)	RR	1.18 (1.02 to 1.37)	42.3
	Antidepressants	Dropout due to AE	PD	All participants	Placebo	8-28	33	7688	430/4718 (9.1)	170/2970 (5.7)	RR	1.49 (1.25 to 1.78)	0.0
Williams, 2017[13]	SSRI	Dropout due to AE	SAnD	All participants	Placebo	16+	24	5131	335/2802 (12.0)	94/2329 (4.0)	RR	2.59 (1.97 to 3.39)	19
	SNRI	Dropout due to AE	SAnD	All participants	Placebo	16+	4	1213	109/663 (16.4)	27/550 (4.9)	RR	3.23 (2.15 to 4.86)	0
	Mirtazapine	Dropout due to AE	SAnD	All participants	Placebo	16+	1	60	2/30 (6.7)	0/30 (0)	RR	5.0 (0.25 to 100.0)	NA
	Buspirone	Dropout due to AE	SAnD	All participants	Placebo	16+	1	30	1/15 (6.7)	0/15 (0)	RR	3.0 (0.13 to 68.26)	NA
Breilmann, 2019[11]	Benzodiazepine	Dropout due to AE	PD	All participants	Placebo	3-15	14	3263	168/1942 (8.6)	54/1321 (4.1)	RR	1.58 (1.16 to 2.15)	0
Williams, 2017[13]	Benzodiazepine	Dropout due to AE	SAnD	All participants	Placebo	16+	2	96	2/47 (4.3)	1/49 (2.0)	RR	1.68 (0.21 to 13.13)	0.0
Bighelli, 2018[11]	Antidepressants	Dropout for any reason	PD	All participants	Placebo	8-28	40	7850	1331/4806 (27.7)	971/3044 (31.9)	RR	0.88 (0.81 to 0.97)	30
Williams, 2017[13]	SSRI	Dropout for any reason	SAnD	All participants	Placebo	16+	26	5208	684/2915 (23.5)	565/2293 (24.6)	RR	1.01 (0.90 to 1.14)	22
Slee, 2019[10]	Citalopram	Dropout for any reason	GAD	All participants	Placebo	Post-tx	2	37	NR	NR	OR	3.62 (0.74 to 20.27)	NR
	Escitalopram	Dropout for	GAD	All	Placebo	Post-tx	13	1581	NR	NR	OR	0.96	NR

Appendix F Table 25. Results for Adverse Events From ESRs of Pharmacologic Treatment of Anxiety Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome	Specific d/o	Population	Control	Followup	k	N analyzed	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
		any reason		participants								(0.76 to 1.16)	
	Fluoxetine	Dropout for any reason	GAD	All participants	Placebo	Post-tx	8	264	NR	NR	OR	1.36 (0.57 to 3.15)	NR
	Paroxetine	Dropout for any reason	GAD	All participants	Placebo	Post-tx	17	1862	NR	NR	OR	1.24 (1.03 to 1.50)	NR
	Sertraline	Dropout for any reason	GAD	All participants	Placebo	Post-tx	6	485	NR	NR	OR	0.94 (0.65 to 1.35)	NR
Williams, 2017[13]	SNRI	Dropout for any reason	SAnD	All participants	Placebo	16+	4	1224	229/663 (34.5)	186/561 (31.5)	RR	0.90 (0.76 to 1.07)	19
Slee, 2019[10]	Duloxetine	Dropout for any reason	GAD	All participants	Placebo	Post-tx	8	1355	NR	NR	OR	1.09 (0.89 to 1.32)	NR
	Venlafaxine	Dropout for any reason	GAD	All participants	Placebo	Post-tx	14	2275	NR	NR	OR	0.98 (0.83 to 1.16)	NR
	Vortioxetine	Dropout for any reason	GAD	All participants	Placebo	Post-tx	4	1074	NR	NR	OR	0.88 (0.67 to 1.15)	NR
	Vilazodone	Dropout for any reason	GAD	All participants	Placebo	Post-tx	3	866	NR	NR	OR	1.59 (1.20 to 2.13)	NR
Williams, 2017[13]	Nefazodone	Dropout for any reason	SAnD	All participants	Placebo	16+	1	105	15/52 (28.8)	7/53 (13.2)	RR	2.18 (0.97 to 4.92)	NA
Slee, 2019[10]	Bupropion	Dropout for any reason	GAD	All participants	Placebo	Post-tx	2	41	NR	NR	OR	0.96 (0.10 to 10.5)	NR
Williams, 2017[13]	Mirtazapine	Dropout for any reason	SAnD	All participants	Placebo	16+	1	60	2/30 (6.7)	1/30 (3.3)	RR	2.0 (0.19 to 20.9)	NA

Appendix F Table 25. Results for Adverse Events From ESRs of Pharmacologic Treatment of Anxiety Compared to Placebo (KQ5)

Author, Year	Intervention	Outcome	Specific d/o	Population	Control	Followup	k	N analyzed	IG n/N (%)	CG n/N (%)	Effect	ES (95% CI)	I^2 (%)
Slee, 2019[10]	Mirtazapine	Dropout for any reason	GAD	All participants	Placebo	Post-tx	10	318	NR	NR	OR	3.36 (0.67 to 19.07)	NR
Imai, 2014[12]	Buspirone	Dropout for any reason (Excl industry funded)	PD	All participants (Excl industry funded)	Placebo	8	2	107	16/52 (30.8)	7/55 (12.7)	RR	2.40 (1.07 to 5.39)	0
Williams, 2017[13]	Buspirone	Dropout for any reason	SAnD	All participants	Placebo	16+	1	30	0/15 (0.0)	3/15 (20.0)	RR	0.14 (0.01 to 2.55)	NA
Imai, 2014[12]	Buspirone	Dropout for any reason	PD	All participants	Placebo	8	3	170	24/86 (27.9)	11/84 (13.1)	RR	2.13 (1.11 to 4.07)	0
Slee, 2019[10]	Buspirone	Dropout for any reason	GAD	All participants	Placebo	Post-tx	6	311	NR	NR	OR	0.76 (0.47 to 1.25)	NR
	Imipramine	Dropout for any reason	GAD	All participants	Placebo	Post-tx	1	26	NR	NR	OR	2.83 (0.74 to 12.10)	NA
	Maprotiline	Dropout for any reason	GAD	All participants	Placebo	Post-tx	1	30	NR	NR	OR	2.32 (0.21 to 26.74)	NA
Williams, 2017[13]	Benzodiazepine	Dropout for any reason	SAnD	All participants	Placebo	16+	3	171	13/86 (15.1)	17/85 (20.0)	MD	0.79 (0.41 to 1.52)	0
Slee, 2019[10]	Benzodiazepine	Dropout for any reason	GAD	All participants	Placebo	Post-tx	15	1019	NR	NR	OR	1.43 (1.12 to 1.86)	NR
Breilmann, 2019[168]	Benzodiazepine	Dropout for any reason	PD	All participants	Placebo	3-15	21	3558	394/2102 (18.7)	504/1456 (34.6)	RR	0.50 (0.39 to 0.64)	62.91

Abbreviations: AE = adverse event; CG = control group; CI = confidence interval; d/o =disorder; Excl = excluded; ES = effect size; ESR = existing systematic review; GAD = generalized anxiety disorder; IG = intervention group; MD = mean difference; NA = not applicable; NR = not reported; OR = odds ratio; PD =

panic disorder; RR = relative risk; SAnD = social anxiety disorder; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; tx = treatment.

Appendix F Table 26. Results of Narrative Syntheses From ESRs of Pharmacologic Treatment of Anxiety (KQ5)

Author, Year	Intervention	Population	Outcome	Findings
Balasubramaniam, 2019[130]	Antidepressants	Older adults	Tolerability	In 5 of 8 trials of escitalopram, citalopram, duloxetine, or venlafaxine compared with a control group, most reported increased side effects with medication; most common side effects were GI-related, fatigue/sedation, and sleep-related.
Viswanathan, 2021[107]	Benzodiazepine	Perinatal	Serious AEs	Evidence was low for an association with spontaneous abortion, NICU admission; evidence was insufficient for preeclampsia, perinatal death, birthweight, Apgar score, infant respiratory distress; evidence was missing for 19 other variables included in the review.
Gupta, 2020[170]	Benzodiazepine	Older adults	Any adverse events	Limited tolerability data showed mild adverse effects such as drowsiness, faintness, and light-headedness were more common with benzodiazepines than placebo. One study reported a serious adverse event (severe gastralgia) in one participant taking a placebo (at 15 days) (k=5 studies total).

Abbreviations: AE = adverse event; ESR = existing systematic review; GI = gastrointestinal; NICU = neonatal intensive care unit.

Appendix G Table 1. Intervention Description of Suicide Risk Screening Studies (KQ1)

Author, Year	IG	Intervention detail	Adherence	Acceptability
Crawford, 2011[175]	IG1	A phone interview was conducted at baseline asking participants about suicidal ideation. In addition to suicidal ideation questions, the 2-item screening questionnaire for depression was repeated; basic demographic data was collected, and participants' mental health was assessed. When participants described thoughts that life was not worth living the researcher made further assessment of suicide risk, encouraged the person to make use of resources already available to them (such as discussing their feelings with healthcare staff), and provided information about helplines and other sources of help. In rare instances where participants reported suicidal plans, the researcher asked for verbal consent to contact clinical staff on their behalf.	NR	NR

Abbreviations: IG = intervention group; NR = not reported.

Appendix G Table 2. Test Accuracy of Screening Instruments to Identify Suicidal Ideation

Screening Test	Author, year	Cutoff	Screened group	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
GDS-15	Heisel, 2010[176]	≥2	Men	0.90 (0.70, 0.97*)	0.59 (0.52, 0.65*)	0.17 (0.11, 0.25*)	0.98 (0.94, 1.0*)	0.902 (0.810, 0.994)
			Women	0.88 (0.76, 0.94*)	0.54 (0.49, 0.59*)	0.21 (0.16, 0.28*)	0.97 (0.93, 0.99*)	0.814 (0.752, 0.877)
			Total	0.88 (0.79, 0.94*)	0.56 (0.52, 0.60*)	0.20 (0.16, 0.25*)	0.98 (0.95, 0.99*)	0.844 (0.793, 0.896)
		≥3	Men	0.90 (0.70, 0.97*)	0.75 (0.69, 0.81*)	0.25 (0.17, 0.37*)	0.99 (0.96, 1.0*)	0.902 (0.810, 0.994)
			Women	0.76 (0.62, 0.85*)	0.70 (0.65, 0.75*)	0.27 (0.20, 0.35*)	0.95 (0.92, 0.97*)	0.814 (0.752, 0.877)
			Total	0.80 (0.69, 0.88*)	0.72 (0.68, 0.76*)	0.26 (0.21, 0.33*)	0.97 (0.94, 0.98*)	0.844 (0.793, 0.896)
		≥4	Men	0.85 (0.64, 0.95*)	0.83 (0.78, 0.88*)	0.32 (0.21, 0.45*)	0.98 (0.95, 0.99*)	0.902 (0.810, 0.994)
			Women	0.57 (0.43, 0.70*)	0.85 (0.81, 0.89*)	0.36 (0.26, 0.47*)	0.93 (0.90, 0.96*)	0.814 (0.752, 0.877)
			Total	0.75 (0.64, 0.84*)	0.82 (0.78, 0.85*)	0.34 (0.27, 0.41*)	0.96 (0.94, 0.98*)	0.844 (0.793, 0.896)
		≥5	Men	0.85 (0.64, 0.95*)	0.92 (0.87, 0.95*)	0.49 (0.33, 0.64*)	0.99 (0.96, 0.99*)	0.902 (0.810, 0.994)
			Women	0.57 (0.43, 0.70*)	0.85 (0.81, 0.89*)	0.36 (0.26, 0.47*)	0.93 (0.90, 0.96*)	0.814 (0.752, 0.877)
			Total	0.65 (0.53, 0.75*)	0.88 (0.85, 0.90*)	0.40 (0.31, 0.49*)	0.95 (0.93, 0.97*)	0.844 (0.793, 0.896)
		≥6	Men	0.65 (0.43, 0.82*)	0.94 (0.90, 0.96*)	0.50 (0.32, 0.68*)	0.97 (0.93, 0.98*)	0.902 (0.810, 0.994)
			Women	0.51 (0.37, 0.64*)	0.89 (0.85, 0.92*)	0.40 (0.29, 0.53*)	0.93 (0.89, 0.95*)	0.814 (0.752, 0.877)
			Total	0.55 (0.43, 0.66*)	0.91 (0.88, 0.93*)	0.43 (0.33, 0.54*)	0.94 (0.92, 0.96*)	0.844 (0.793, 0.896)
GDS-SI	Heisel, 2010[176]	≥1	Men	0.80 (0.58, 0.92*)	0.81 (0.75, 0.86*)	0.28 (0.18, 0.41*)	0.98 (0.94, 0.99*)	0.857 (0.745, 0.969)
			Women	0.80 (0.66, 0.89*)	0.80 (0.76, 0.84*)	0.36 (0.28, 0.46*)	0.97 (0.94, 0.98*)	0.822 (0.751, 0.893)
			Total	0.80 (0.69, 0.88*)	0.80 (0.77, 0.84*)	0.34 (0.27, 0.41*)	0.97 (0.95, 0.98*)	0.834 (0.774, 0.894)

Appendix G Table 2. Test Accuracy of Screening Instruments to Identify Suicidal Ideation

Screening Test	Author, year	Cutoff	Screened group	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
		≥2	Men	0.65 (0.43, 0.82*)	0.95 (0.91, 0.97*)	0.54 (0.35, 0.72*)	0.97 (0.93, 0.98*)	0.857 (0.745, 0.969)
			Women	0.51 (0.37, 0.64*)	0.92 (0.88, 0.94)	0.46 (0.34, 0.59*)	0.93 (0.90, 0.95*)	0.822 (0.751, 0.893)
			Total	0.55 (0.43, 0.66*)	0.93 (0.90, 0.95*)	0.49 (0.38, 0.60*)	0.94 (0.92, 0.96*)	0.834 (0.774, 0.894)
		≥3	Men	0.50 (0.30, 0.70*)	0.99 (0.96, 1.0*)	0.81 (0.50, 0.92*)	0.97 (0.92, 0.98*)	0.857 (0.745, 0.969)
			Women	0.29 (0.18, 0.42*)	0.97 (0.95, 0.99*)	0.61 (0.41, 0.78*)	0.91 (0.87, 0.93*)	0.822 (0.751, 0.893)
			Total	0.35 (0.25, 0.47*)	0.98 (0.96, 0.99*)	0.67 (0.50, 0.80*)	0.92 (0.90, 0.94*)	0.834 (0.774, 0.894)
SDDS-PC - Feeling suicidal	Olfson, 1996[22]	Answered affirmatively	Total	0.83 (0.62, 1.0)	0.98 (0.97, 0.99)	0.30 (0.15, 0.46)	1.0 (0.99, 1.0)	NR
SDDS-PC - Thoughts of death	Olfson, 1996[22]	Answered affirmatively	Total	1.00 (0.76, 1.0*)	0.81 (0.78, 0.84)	0.06 (0.03, 0.09)	1.0 (1.0, 1.0*)	NR
SDDS-PC - Wishing you were dead	Olfson, 1996[22]	Answered affirmatively	Total	0.92 (0.76, 1.0)	0.93 (0.92, 0.95)	0.14 (0.06, 0.22)	1.0 (0.99, 1.0)	NR
Suicide Risk Assessment Tool	Desjardins, 2016[23]	Moderate or High Risk	ED	0.42 (0.19, 0.68)*	0.98 (0.94, 1.0)*	0.71 (0.36, 0.92)*	0.94 (0.88, 0.97)*	NR
		High Risk	ED	0.67 (0.21, 0.94)*	0.99 (0.95, 1.0)*	0.67 (0.21, 0.94)*	0.99 (0.95, 1.0)*	NR

*Calculated.

Abbreviations: AUC = area under curve; CI = confidence interval; ED = emergency department; GDS = Geriatric Depression Scale; GDS-SI = Geriatric Depression Scale – Suicide Ideation; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; SDDS-PC = Symptom Driven Diagnostic System for Primary Care; SE = standard error.

Appendix G Table 3. Detailed Participant Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	BL MH status
Borschmann, 2013[177]	35.8 (≥18)	80.7	High school grad: NR College grad: NR	Employed: 11.4 Single: 85.2 Other SES: Permanently disabled: 47.7%	Black: 10.2 Latinx: NR Asian/AA: 1.1 Native Am/AN: NR White: 73.9	HADS, depression subscale >10: 65.9% AUDIT score >15: 39.8%
Bruce, 2004[178]	NR (60-94)	71.57	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: Poverty status: 3.8%	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: 71.6	MDD: 66.2%
Bush, 2017[179]	47.6 (NR)	31.36	High school grad: 11 College grad: 42.37	Employed: NR Single: 38.8 Other SES: NR	Black: NR Latinx: 7.6 Asian/AA: NR Native Am/AN: NR White: 72	MDD: 83.0% Substance use disorder, past 6 mo: 16.1% Alcohol use disorder, past 6 mo: 22.9%
Carter, 2010[180]	24.5 (18-65)	100	High school grad: 22.9 College grad: NR	Employed: 18.6 Single: 55.7 Other SES: Secondary educ. not completed: 34.3%	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	Any anxiety disorder: 88.6% Any substance use disorder dx: 68.6%
Davidson, 2006[181]	31.9 (18-57)	84.0	High school grad: 38.7 College grad: 6.6	Employed: 32.1 Single: 79.2 Other SES: Any benefits: 84.0%	Black: 0 Latinx: 0 Asian/AA: 0 Native Am/AN: 0 White: 100	NR
Franklin, 2016[182]	24.5 (≥18)	NR	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: NR	Black: 1.8 Latinx: 6.1 Asian/AA: 4.9 Native Am/AN: 1.2 White: 82.2	Psychiatric medication: 42.9%

Appendix G Table 3. Detailed Participant Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	BL MH status
Goodman, 2016[183]	38.3 (18-55)	33	High school grad: 68.1 College grad: 7.7	Employed: 25.3 Single: NR Other SES: Hollingshead-Redlich Social class: 2: 2.2%; 3: 17.6%; 4: 80.2%	Black: 31.9 Latinx: 45.1 Asian/AA: 1.1 Native Am/AN: 1.1 White: 14.3	MDD: 63.7%
Jobes, 2017[184]	26.8 (18-48)	19.6	High school grad: 39 College grad: 7.5	Employed: NR Single: 26.0 Other SES: NR	Black: 24 Latinx: 3.6 Asian/AA: 11 Native Am/AN: NR White: 53	Depressive disorder: 62.6% Anxiety disorder excluding PTSD: 48.9% Drug abuse or dependence: 4.3% Alcohol abuse or dependence: 15.8%
Katz, 2022[185]	42.8 (NR)	15.8	High school grad: 20.4 College grad: 26.4	Employed: NR Single: 62.0 Other SES: NR	Black: 16.0 Latinx: 14.8 Asian/AA: 2.3 Native Am/AN: 1.7 White: 72.6	MDD: 84.6% Alcohol abuse or dependence: 48.4% Other substance abuse or dependence: 36.4%
Kovac, 2002[186]	23 (18-42)	72.7	High school grad: 100 College grad: 1.7	Employed: NR Single: 86 Other SES: Edu: All undergraduate college students	Black: 22.3 Latinx: NR Asian/AA: NR Native Am/AN: NR White: 74.4	Previous treatment for depression: 54%

Appendix G Table 3. Detailed Participant Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	BL MH status
Linehan, 2006[187]	29.3 (18-45)	100	High school grad: 16.8 College grad: 23.8	Employed: NR Single: 87.2 Other SES: Annual income, $:30-50K: 9.9%	Black: 4.0 Latinx: NR Asian/AA: 2.0 Native Am/AN: 1.0 White: 87.0	MDD: 72.3% Anxiety disorder: 55.4% Any substance use disorder dx: 29.7%
McMain, 2017[188]	29.67 (18-60)	78.6	High school grad: 9.5 College grad: 50	Employed: 34.5 Single: NR Other SES: NR	Black: NR Latinx: NR Asian/AA: NR Native Am/AN: NR White: NR	MDD: 51.2% Anxiety disorder: 60.7% Any substance use disorder dx: 69.1%
Mühlmann, 2021[189]	33.6 (18+)	70.9	High school grad: NR College grad: 19.6	NR	NR	MDD: 80%
Pigeon, 2019[190]	54.8 (18-70)	20	High school grad: 38.0 College grad: 12.0	Employed: NR Single: 14.0 Other SES: NR	Black: NR Latinx: 4.0 Asian/AA: NR Native Am/AN: NR White: NR	NR
Pistorello, 2012[191]	20.86 (18-25)	81.0	High school grad: 100 College grad: NR	Employed: NR Single: NR Other SES: Edu: All college students	Black: 3.2 Latinx: 11.1 Asian/AA: 6.3 Native Am/AN: 4.8 White: 69.8	MDD: 81.0% Anxiety disorder: 79.4% Any substance use disorder: 36.5%
Pistorello, 2021[192]	20 (18-25)	67.7	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: NR	Black: 3.2 Latinx: 8.1 Asian/AA: 16.1 Native Am/AN: NR White: 48.4	NR

Appendix G Table 3. Detailed Participant Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	BL MH status
Priebe, 2012[193]	32.2 (16+)	87.5	High school grad: NR College grad: NR	Employed: 46.3 Single: NR Other SES: NR	Black: 15 Latinx: NR Asian/AA: 21.3 Native Am/AN: NR White: 57.5	NR
Riblet, 2022[194]	51.5 (18+)	35	High school grad: NR College grad: NR	Employed: NR Single: 35 Other SES: NR	Black: 5 Latinx: 5 Asian/AA: NR Native Am/AN: NR White: 85	Depressive disorder: 70% Anxiety disorder: 45% Substance related and addictive disorders: 10%
Simon, 2022[195]	NR (18+)	67.3	High school grad: NR College grad: NR	Employed: NR Single: NR Other SES: NR	Black: 4.0 Latinx: 8.4 Asian/AA: 3.4 Native Am/AN: 0.7 White: 74.7	Depression dx in past year (EHR): 65.2% Anxiety d/o dx in past year (EHR): 59.2% DUD in past year (EHR): 7.4% AUD in past year (EHR): 5.9%
Torok, 2022[196]	21.5 (18-25)	84.6	High school grad: 24.0 College grad: 29.7	Employed: 63.1 Single: NR Other SES: NR	NR	NR
Van Orden, 2021[197]	72 (>=60)	68	NR	NR	Black: 4.8 Latinx: NR Asian/AA: NR Native Am/AN: 1.6 White: 92	Current antidepressant prescriptions: 43.6%

Appendix G Table 3. Detailed Participant Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	Mean Age (Range), years	% Women*	Education	Other SES	Race or Ethnicity	BL MH status
van Spijker, 2014[198]	40.9 (NR)	66.1	NR	Employed: 50.0 Single: NR Other SES: NR	NR	Depressive symptoms: 27.1% Anxiety symptoms: 10.4%
Ward-Ciesielski, 2017[199]	40.2 (≥18)	37	High school grad: 14 College grad: 20	Employed: NR Single: 65 Other SES: Homeless (lifetime): 54%; Annual income: <$10K: 43% $10-24,999: 38% $25-50K: 16% >$50K: 3%	Black: 9 Latinx: NR Asian/AA: 1 Native Am/AN: 2 White: 84	Psychiatric medications: 16%

*****Gender was not reported in studies of perinatal patients so participants are counted as women, recognizing that there may be some individuals who do not identify as women; non-binary/gender non-conforming categories were not reported in any studies.

Abbreviations: AA = Asian American; AN = Alaska Native; AUDIT = Alcohol Use Disorders Identification Test; BL MH = baseline mental health; HADS = Hospital Anxiety and Depression Scale; MDD = major depressive disorder; Native Am= Native American; NR = not reported; PTSD = post-traumatic stress disorder; SES = socioeconomic status.

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
Borschmann, 2013[177]	IG1	Participant met with their care coordinator to have a facilitated, informed discussion about the most appropriate information to include in their joint crisis plan (JCP). A list of topics to be considered in the participant's JCP included "Positive things I can do in a crisis," "Specific refusals regarding treatment during a crisis," "Practical help in a crisis," and "Useful telephone numbers." Other key workers, advocates, friends, or family members were also invited to the meeting at the discretion of the participant. Meeting lasted approximately 60 min and the final information included in the JCP was of the participant's choosing and was entered in the participant's own wording. Within 24 hours of the meeting, a typed version of the JCP was distributed to all individuals specified by the participant. If the participant gave permission, a copy of the JCP was also attached to their electronic medical records in order to maximize dissemination of the plan within the local mental health trust.	89.1% attended joint crisis plan meeting	16 (47.1%) reported that using their joint crisis plan had contributed to having a greater feeling of control over their problems; 47.1% reported that joint crisis plan had contributed to an improved relationship with their mental health team; and 29 (85.2%) stated that they would recommend using a joint crisis plan to other service users
Bruce, 2004[178]	IG1	1) Application of clinical algorithm for treating geriatric depression in a primary care setting (recommends first-line treatment of an SSRI); 2) Treatment management by depression care managers that collaborated with physicians to help them recognize depression, offer guideline-based treatment recommendations, monitor clinical status, and provide appropriate followup. The depression care manager	30.9% dropped out of the intervention over 12 months	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		interacted with patients in person or by telephone at scheduled intervals, or when clinically necessary, to monitor depressive symptoms, medication adverse effects, and treatment adherence.		
Bush, 2017[179]	IG1	Participants assigned to the VHB condition downloaded and used the Virtual Hope Box (VHB) app. The VHB contains six primary sections constructed to collectively provide support, comfort, distraction, or relaxation by using audio, video, pictures, games, mindfulness exercises, messages, inspirational quotes, coping statements, and other media content. A provider works with a patient to populate the sections to support the patient's individual needs. The patient then can use the VHB away from the clinic and modify the VHB content in response to changing needs. Length of intervention: 12 weeks.	NR	84% of intervention participants reported the study materials to be somewhat or very helpful, compared to 44% of control group participants.
Carter, 2010[180]	IG1	Participants participated in dialectical behavior therapy (DBT), a team-based approach, including individual therapy, group-based skills training, and telephone access to an individual therapist. The relevant skills training group were supervised by a group therapist and met weekly with the modules running in the following order: Interpersonal Effectiveness, Emotion Regulation and Distress Tolerance. Each module ran for 8 weeks. Groups had a minimum of four members before commencement and a maximum of eight members. Entry to the skills group occurred only at the	NR	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		commencement of the next skills module.		
Davidson, 2006[181]	IG1	CBT focuses on the patient's core beliefs and overdeveloped behavioral patterns that impair adaptive functioning. Interventionists aimed to deliver up to thirty sessions of CBT over 1 year, each session lasting an hour. Providing that a patient was not immediately suicidal at entry into the trial, therapists first developed an agreed formulation of the patient's problems, then, priority was given to the goals agreed between therapist and patient to improve adaptive functioning. In CBT, patients develop new, more adaptive beliefs about self and others and work on developing underdeveloped behavioral strategies to promote improved levels of social and emotional functioning. All trial participants randomized to CBT also received the treatment they would have received if the trial had not been in place.	Offered on average 27 (standard deviation [SD], 13) sessions of CBT to the patients in the trial (median, 31; range, 1 to 49). An average of 16 (SD, 12) sessions was attended (median, 15; range, 0 to 35). An average of 8 (SD, 8) sessions was refused (median 5).	NR
Franklin, 2016[182]	IG1	Brief (1-2 min), game-like app called Therapeutic Evaluative Conditioning (TEC), designed to increase aversion to SITBs and decrease aversion to the self. Designed to be a brief, game-like treatment that could be accessed by any device with an internet connection. It was aimed for TEC to be accessed multiple times a day at the convenience of the user. Several TEC characteristics promoted this aim: It takes 1 to 2 min to complete a single instance of TEC; TEC becomes more challenging as the trials progress; points are awarded for faster	78.5% of participants accessing the TEC app at least once during the first month; 36.0% accessed the app during the 2nd month. (Results not retained beyond 4 weeks because of high attrition)	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		and more accurate performance; each instance of TEC is unique, increasing replay value; and although TEC was primarily intended as a mobile app, it includes a responsive design that allows it to automatically format itself for phones, tablets, laptops, and desktops. Included a version of TEC that targeted self-related words (e.g., me, myself, I, mine) and Self-injurious thoughts and behaviors (SIBT)-related stimuli that primarily depicted suicide/death stimuli, including: SITB stimuli related to pill overdose (n =4), hanging (n =2), jumping from heights (n =2), pointing a gun at one's own head (n =2), self-cutting (n 2), skulls/bones (n 2), and the words "death" and "suicide." All stimuli were either created by the group (words and self-cutting pictures), taken from the IAPS, or Creative Commons Zero images from the Internet.		
Goodman, 2016[183]	IG1	Participants randomized to DBT received standard DBT treatment for 6 months, including weekly skills training group (90 min), weekly individual treatment (50-60 min), and telephone coaching as needed.	The mean (SD) duration in treatment was 17.9 (11.5) weeks	NR
Jobes, 2017[184]	IG1	Soldiers were offered clinical care guided by the Collaborative Assessment and Management of Suicidality (CAMS) approach. CAMS is a suicide-specific therapeutic framework that employs the use of a multipurpose assessment, treatment-planning, tracking, and outcome tool called the Suicide Status Form (SSF). Central to CAMS is an empathic and collaborative assessment	93% of participants completed planned minimum 4 sessions. 44% received additional post-treatment sessions.	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		and treatment-planning approach to suicide risk throughout care. Starting at the index session, CAMS uses the CAMS Stabilization Plan to reduce access to lethal means and increase coping strategies; CAMS also targets and treats patient-defined suicidal "drivers" using appropriate clinical interventions (e.g., exposure treatment for a posttraumatic stress disorder [PTSD]-related driver or couples therapy for a marriage-related driver). CAMS is concluded after three consecutive sessions when suicidal thoughts, feelings, and behaviors are successfully managed per CAMS resolution criteria.		
Katz, 2022[185]	IG1	Receive extended-release lithium carbonate, in addition to usual VA management beginning at a dose of 600 mg/d (300 mg/d if there were contraindications to this dose) and titrated upward or placebo (98% microcrystalline cellulose). Lithium serum concentrations were determined by a central laboratory after each dose adjustment until steady state with a lithium concentration between 0.6 and 0.8 mEq/L (to convert to millimoles per liter, multiply by 1). If participants could not tolerate the dose needed to achieve the target concentration, they were given the maximum tolerated dose, at least 300 mg/d. Real or simulated lithium concentrations, creatinine concentration, estimated glomerular filtration rate, and review of symptoms were used to guide	Only 1074 of 2154 lithium concentrations (49.9%) were 0.5 mEq/L or greater. Only 88 of 519 participants (17.0%) took 80% or more of their study medication (46 in the lithium group) and were considered substantially adherent. Mean (SD) treatment exposure was 6.7 (4.5) months for participants with major depression and 5.6 (4.6) for participants with bipolar disorder. Overall, mean (SD) lithium levels, including titration, were mean 0.42 (0.29) mEq/L, with means (SDs) at 3 months of 0.54 (0.25) mEq/L for patients with bipolar disorder and 0.46 (0.30) mEq/L for patients with major depressive disorder (n = 255; P = .11). Participants in both study assignment groups had a mean (SD) of 1.15 (0.23) mental health service visits per month,	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		dosing by study physicians at each site. Medications were dispensed in blister cards that contained 1- or 2-week supplies. After steady state was achieved, lithium concentrations were determined monthly for 6 months and then quarterly. Lithium concentrations were measured more frequently if there were interacting medications or side effect concerns. Usual VA MH care: Study medications were added to usual VA mental health care, including medications and psychosocial treatment for mental health conditions and a range of rehabilitation- and recovery-oriented services.	without differences in treatment group, and 10 to 12 study visits during the year.	
Kovac, 2002[186]	IG1	Cognitive change group: Four 20-min writing sessions over 2 weeks. Writing instructions were to describe a difficult time(s) in their life (e.g., when a person felt most suicidal, depressed, or upset) and focus on interpreting thoughts and feelings about difficult time; continuous reinterpretation of the event, thoughts and feelings (i.e., keep writing about their thoughts and feelings for full time period even if they feel they have completed all they want to say).	NR	Those in IG1 rated the value of the experiment significantly higher than did the controls (p=0.025)
Linehan, 2006[187]	IG1	Dialectical behavior therapy: CBT program to treat suicidal clients meeting criteria for BPD; targets suicidal behavior, behaviors that interfere with treatment delivery and other dangerous, severe, or destabilizing behaviors. Address five functions: 1) increasing behavioral capabilities; 2) improving motivation for skillful behavior; 3) assuring	Median sessions delivered: 42.5 (individual), 38.8 (group)	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		generalization of gains to natural environment; 4) enhancing therapists' capabilities and motivation to treat patients effectively. Composed of weekly individual psychotherapy (1 hour); weekly group skills training (2.5 hours); telephone consultation as needed; and weekly therapist consultation team meetings.		
McMain, 2017[188]	IG1	The DBT group skills training consisted of the manualized approach developed by Linehan, adapted to a 20-week curriculum in which groups meet for 2 hours weekly. The training uses a psycho-educational focus to enhance capabilities. The following five modules were covered: mindfulness, emotion regulation, distress tolerance, interpersonal effectiveness and dialectics. Prior to the first group meeting, participants attended a 90-min individual orientation session. Skills group leaders were not available to provide crisis coaching outside of skills group sessions. Participants were encouraged to have a therapist or another individual (e.g., family practitioner, spiritual counsellor, family member) who could provide crisis support. Additionally, participants were offered a list of resources for crisis support (e.g., crisis call lines, distress centres).	71% completed the treatment. Treatment completers attended a mean of 17.9 sessions (SD, 1.6), while those who dropped out attended a mean of 5.6 (SD, 5.9).	NR
Mühlmann, 2021[189]	IG1	Self-help program "Living under control" (translated into Dutch): Accesses via website, primarily based on CBT. Consisted of 6 modules, an "acute help" page where psychiatric hospitals and suicide prevention clinics were listed, a	47/196 (24%) participants in the IG received a phone call due to inactivity	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		"my profile" page, and a messaging system. Each module contained a theoretical introduction, several exercises, and a FAQ section. Every week, a new module was released to the participant. Approximately 10 days into the program, the participants received a message from the research team, encouraging them to write if they have any questions related to the exercises. Responding to the message was optional. The modules remained available to participants also after the 6-week study period.		
Pigeon, 2019[190]	IG1	Brief cognitive behavioral therapy for insomnia (bCBTi): All participants in the bCBTi condition were encouraged to begin or continue TAU except for insomnia interventions. In addition, participants received four individual sessions of bCBTi. Behavioral health providers with at least a master's degree in mental health counseling, social work, or psychology were trained to deliver bCBTi. Sessions typically occurred weekly for the first 3 weeks, with 2 weeks between the third and fourth sessions. bCBTi consisted of standard, structured, multicomponent CBT-I intervention containing sleep education, sleep hygiene, sleep restriction, stimulus control, and cognitive therapy. Participants completed a daily sleep diary for the week prior to treatment initiation and throughout the intervention period. Sleep efficiency (total sleep time divided by total sleep opportunity) is calculated by	Mean (SD) sessions attended = 1.5 (1.6); 70% received some mental health treatment outside of the study, with no difference across groups	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		the therapist each week and is used to guide the sleep restriction portion of bCBTi. Values are summed and averaged over a 1-week period to guide bCBTi treatment.		
Pistorello, 2012[191]	IG1	The DBT treatment provided as part of this study followed closely the standard outpatient DBT package (Linehan, 1993a, b): 1) weekly 50-minute individual psychotherapy (while student was in town); 2) weekly 90-minute group skills training; 3) skills coaching as needed (via telephone, email, or texting) between sessions to help patients generalize skills as solutions to their difficulties (Linehan, 1993a); 4) weekly 90-minute group supervision/ consultation for therapists; and 5) as-needed family interventions (Fruzzetti, Santisteban, & Hoffman, 2007).	35% dropped out before completing 7 months of therapy, 19% completed between 7 and 11 months, and 45% remained in treatment for the entire 12 months.	NR
Pistorello, 2021[192]	IG1	Treatment lasted from 4-8 weeks, depending on clients' response to care. This treatment length was chosen because it is consistent with college counseling centers' (CCCs') average number of 5.61 sessions as well as CAMS data demonstrating that "acute resolvers" improve after about six sessions or fewer. The variability allowed for tailoring to client needs. The original Collaborative Assessment and Management of Suicidality (CAMS) treatment manual was primarily used, but more recent updates were also included. Each CAMS session started with the collaborative completion of an SSF by client/therapist, which varies in content	Most participants (66%) completed all eight sessions (M = 6.76, SD = 2.32). Overall average therapist adherence rating for the CAMS condition exceeded the required score of 3 (M = 4.32; SD = 1.54).	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		depending on the stage of treatment (first session vs. interim/tracking sessions vs. final outcome/disposition session). In turn, all CAMS sessions across care ended with a reconsideration of the CAMS Stabilization Plan and the driver-focused treatment plan. The first four sessions conducted by each study counselor (and additional randomly selected sessions) were rated for adherence using the CAMS Rating Scale by reviewing digitally recorded sessions. Study therapists were seven current on-site staff members (four licensed psychologists, two postdoctoral fellows, and one social work intern) interested in learning new treatment approaches for suicidal clients. Study therapists varied in theoretical orientation, professional discipline, and stage of training; none were familiar with CAMS prior to this study. CAMS training for therapists entailed reading the CAMS manual, attending a two-day role-play training, and weekly phone consultations with the developer of CAMS.		
Priebe, 2012[193]	IG1	Patients randomized to DBT received 12 months of DBT delivered according to Linehan's treatment and skills training manuals. DBT is based on the principles of cognitive behavioral therapy with the inclusion of mindfulness, validation, and supportive therapy techniques, and holds as its core the key dialectic of the acceptance of the individuals as they are with the acknowledgement of the need for change. It consists of weekly hour-long	Of the 18 patients allocated to DBT who started treatment but did not complete, seven ceased treatment in the first 3 months, three between 4 and 6 months, six between 7 and 9 months, and two in the last 3 months of treatment. Their mean length of stay in treatment was 5.7 months (SD, 3.2).	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		individual therapy sessions, a weekly 2-hour skills training group, and out-of-hours skills coaching over the telephone as needed.		
Riblet, 2022[194]	IG1	VA BIC is a manualized intervention that includes conversation guides to facilitate the session. Program is 3 months, adapted to help bring the program to scale in a clinical setting. The patient was contacted by the interventionist by phone to briefly introduce them to VA BIC, and to schedule the brief education visit. A packet of printed educational materials was mailed out to the patient in anticipation of the visit. The patients then received a 1-hour, one-on-one educational intervention on suicide prevention either over phone or video. As part of this session, the interventionist also introduced patients to safety planning. Patients then received six additional contacts with the interventionist over the course of 3 months. These visits occurred over phone or video. During these sessions, the interventionist checked on the patient's wellbeing, encouraged self-monitoring of symptoms, affirmed progress, reviewed the safety plan, assessed adherence with treatment, and continued to build the patient's sense of self-efficacy and motivation for treatment engagement. VA BIC aims to educate patients about suicide prevention, bolster self-efficacy, and treatment engagement. A primary focus of the intervention is to encourage and	NR	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		facilitate treatment engagement and social connection. It incorporates aspects of motivational interviewing. It can be delivered by a trained mental health provider such as a psychologist, social worker, or mental health nurse. The role of the interventionist can be best defined as that of a coach whose goal is to help patients stay connected to their treatment. The sessions do not include mental health interventions such medication management or psychotherapy, rather it uses a standardized approach to encourage connection between the patient and the primary treatment team. Prior to the start of the study, the interventionist, a clinical psychologist by training, was formally trained in the delivery of VA BIC through didactics and video demonstrations.		
Simon, 2022[195]	IG1	A structured care management program (delivered by online messaging and/or telephone) included motivational interventions to promote engagement in recommended treatment pathways and coordination of care with responsible providers. Intervals between outreach contacts varied according to C-SSRS risk level at last contact, ranging from 1 week or less for participants reporting suicidal intent with a specific plan to 2 months or more for participants reporting no recent suicidal ideation. Care managers' followup messages included both motivational enhancement and care navigation to promote recommended	Approximately 31% of those offered care management initially accepted the invitation, and approximately 17% remained engaged for over 9 months.	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		outpatient care. Care managers regularly communicated risk assessment results and followup recommendations to treating outpatient clinicians who were responsible for all decisions regarding specific treatments using provider-to-provider messaging within the Epic EMR. Messages were clearly labeled as informational only ("FYI") or requests for specific action. Direct telephone communication was used for communication of urgent needs. Care managers also communicated directly with primary care and mental health nursing staff and reception/appointing staff (using EMR-based messaging or telephone) to facilitate recommended followup care. The purpose of the intervention is to prompt appropriate followup treatment by responsible outpatient providers. Care managers served as treatment facilitators rather than direct treatment providers. Study care managers were master's degree–level mental health clinicians who received 14 hours of intervention-specific training followed by twice-monthly supervision teleconferences with investigators. IG1 was supplemental to usual care, and participants assigned to either intervention group were free to receive any non-study mental health or general medical services normally available.		

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
Simon, 2022[195]	IG2	The skills training program, drawing from skills training in traditional DBT, included an interactive online program supported by a skills coach. The online program included video instruction introducing and demonstrating 4 specific DBT skills: mindfulness, mindfulness of current emotion, opposite action, and paced breathing. Skills coaches did not provide psychotherapy but sent EHR portal messages to reinforce each visit to the online program and encourage practice of specific skills as well as outreach messages to participants without recent visits. Frequency of outreach depended on each participant's level of involvement but was at least monthly during the initial 6 months. All skills coaches had completed mental health bachelor's degree coursework and received 14 hours of initial intervention-specific training followed by twice-monthly supervision teleconferences with investigators. Study care managers were master's degree–level mental health clinicians who received 14 hours of intervention-specific training followed by twice-monthly supervision teleconferences with investigators. Motivational Interventions – Coaching protocols will include scripted messages for motivational assessment and motivational enhancement based on those used successfully in our previous outreach and coaching programs. These messages will focus on specific behavioral goals (initial enrollment in	Of those offered skills training, 39% accepted the invitation, but only 2% remained engaged for over 9 months.	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		online program, completion of specific online modules, practice of emotion regulation skills). Messages will be suitable for delivery either by telephone or online messaging. Integration with usual care: as described above, coaches will communicate with treating mental health and/or general medical providers following each participant's enrollment in the online program. These standardized messages will briefly describe the program content, invite treating clinicians to reinforce use of programs skills, and invite treating clinicians to contact the care manager for additional information. Because the coaching program does not include specific recommendations regarding followup treatment, messages from coaches will not include recommendations for providers. If, however, coaching contacts discover clear need for evaluation or intervention by mental health or general medical providers, coaches will communicate that need to participants and providers and will facilitate necessary followup care. Management of clinical emergencies: the coaching program does not include specific assessment of suicidal ideation or suicidal behavior. Nevertheless, it is possible that coaching contacts may discover need for urgent or emergent intervention. For emergent needs, all health systems have capacity for in-person emergency department assessment, 24-hour consultation with		

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		on-call mental health providers, and mobile crisis teams. Coaching algorithms will include specific recommendations for use of these services. IG2 was supplemental to usual care, and participants assigned to either intervention group were free to receive any non-study mental health or general medical services normally available.		
Torok, 2022[196]	IG1	Brief, 7-module, self-guided DBT smartphone application ("LifeBuoy") designed to improve emotional regulation and increase distress tolerance skills. The frequency of the modules was flexible; however, participants needed to complete one module to unlock the next. Participants were able to return to modules as often as desired, with each estimated to approximately 5 minutes to complete. One DBT skill was introduced and practiced per module, with brief education content provided at the start of each module to explain the skill, followed by an interactive exercise or feature to practice the skill, such as quizzes, a brief animated breathing tool, and audio files for guided mindfulness and self-soothing. All interactive features were built into the application for ease of access. Following the exercise component of the module, participants were presented with a brief overview of the importance of that skill in the context of managing suicidal thoughts and tips as to the frequency with which the skill should be practiced before exiting the module. The skills taught were self-	96% of participants downloaded the app; mean number of modules completed = 6.84, SD = 4.30; proportion who completed 5 or more modules = 71.5%	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		soothing, pros and cons, distress tolerance, Activities, Contributing, Comparisons, Emotions, Push away, Thoughts, and Sensation (ACCEPTS), and radical acceptance. The ACCEPTS skill was delivered across 2 modules. The final module focused on values and goal setting, providing a behavioral activation strategy to encourage participants to engage in activities that enhance their sense of purpose, pleasure, and provide a sense of mastery of the skills taught in the preceding modules. In this module, participants were asked to identify the top 3 values important to them (out of a predefined list of 10) and then set a goal against each one to achieve over the course of the 6 weeks. Weekly reminders were sent to encourage participants to achieve their goals. The application also contained a toolbox function that provided access to additional distress tolerance activities (i.e., Temperature, Intense exercise, Paced breathing, Paired muscle relaxation [TIPP]) and built-in distraction tools (e.g., a popping bubbles game or a fun quiz) as well as a mood tracker. The modules were presented as islands on a map (S1 Fig), and progress was signaled by the islands changing from being whited out to technicolor. To support participant safety during the trial, they built in a linked directory of major Australian crisis helplines (e.g., Lifeline and Suicide Call Back Service) into each application, along with a “help” button that, if pressed, sent		

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		an email to the research team that the participant wanted to be contacted by the clinical psychologist within the next 24 business hours. At each survey time point, if participants exceeded cutoff scores of 21 or greater on the Suicidal Ideation Attributes Scale (SIDAS), the research team was alerted via email. In tandem, the participant was sent an alert flagging their score and asking if they wanted to be contacted by the team's clinical psychologist. If the participant returned a "yes" response, they were contacted by phone within 72 hours.		
Van Orden, 2021[197]	IG1	"Social Engage" (S-ENG): involved up to 10 in-home individual sessions over approximately 10 weeks. The manual was adapted from Engage for late-life depression by the lead author, with input from an Engage developer (co-author PA). Engage, as originally developed, coaches patients to re-engage with pleasant, physical, or social activities they may have stopped doing in the context of depression. Subjects create "action plans" that involve setting a goal, brainstorming ways to achieve the goal, and selecting specific actions to take before their next session. Therapists follow up at subsequent sessions for each action plan, including whether it was completed (i.e., participants engaged in planned activities). Engage is a stepped, modular intervention that addresses barriers to action plan implementation and	All participants completed at least one session; over half (66%) completed 10; most completed at least 6 (88%). Review of therapist notes indicated that all action plans addressed social engagement; the majority of participants (96%) successfully completed at least one planned social activity, consistent with increases in social engagement. Therapists coached participants to transform goals focused on pleasant/physical activities to "make them social" (e.g., attend an exercise class or walk with a friend). The majority (90%) focused at least one action plan on non-family connections and 25% focused at least one on family relationships.	Themes of feedback: 1) increased insight into the importance of social connection; 2) value of using action plans to be proactive and intentional with social engagement (e.g., reaching out, joining groups, utilizing supports such as transportation assistance); 3) utility of "barrier strategies" to

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		challenges in processing positive outcomes when exposed to rewarding activities. Barriers addressed are negativity bias, affect regulation, and apathy. When barriers are identified, simple behavioral interventions to address barriers are added to action plans. Modifications for this study were minimal and involved adapting psychoeducational materials to address the importance of social connection, adding a values clarification exercise on aspects of connection most important to participants, and instructions to therapists to focus action plans on social engagement.		overcome negative self-talk, low self-esteem, and anxiety. Several (30%) noted the utility of accountability for social engagement and reported plans to start psychotherapy or support groups. Participants appreciated information on local opportunities for social engagement.
van Spijker, 2014[198]	IG1	The main goal of this intervention is helping participants decrease the frequency and intensity of their suicidal thoughts. Content was developed with the help of an expert team consisting of clinical psychologists and psychiatrists experienced in the treatment of suicidal people. A focus on controlled thinking, rather than thought cessation, should lead to reduced suicidal thinking. It consists of six modules, focusing on 1) the repetitive character of suicidal thoughts, 2) regulating intense emotions, 3) identifying automatic thoughts, 4) thinking patterns,	22.4% never started the program, 21.6% completed 1 or 2 modules, 56% completed 3-6 modules. Reported average of 15 min/day spent on intervention.	NR

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
		5) thought challenging, and 6) relapse prevention. Each module contains a theory section, a weekly assignment, a few “core exercises” and several “optional exercises.” For example, the first module explains that suicidal thoughts can develop out of self-protection, as keeping on living may seem worse than dying. Similarities between worry and suicidal thinking are also outlined. The weekly assignment involves tallying suicide related thoughts to obtain an idea of how often these occur, while the core exercises aim at learning to manage these repetitions better by introducing worry postponement. The optional exercises contain other strategies for managing suicidal thoughts, such as positive worrying, attentive breathing and seeking distraction. Participants follow one module per week and can receive up to six motivating automated e-mails. There is a FAQ function on the website via which questions can be asked. Participants are encouraged to complete one module per week and ideally spend 30 minutes per day on the program. A paper version of the intervention was given to five patients attending an outpatient mental health treatment facility in Amsterdam to obtain feedback, after which final improvements were made and the website was developed.		

Appendix G Table 4. Detailed Intervention Characteristics Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year	IG	Intervention detail	Adherence	Acceptability
Ward-Ciesielski, 2017[199]	IG1	Initially, participants were asked to briefly describe the factors they believed to be associated with their suicidal ideation and any patterns they had noticed in the occurrence of the ideation. At the end of each session, participants were provided an individualized list of mental health resources (e.g., community mental health centers, private practitioners), based primarily on financial and geographic considerations DBT Brief Suicide Intervention (DBT-BSI): designed to last 45–60 min; presented participants with five DBT skills: mindfulness, mindfulness of current emotions, opposite-to-emotion action, distraction, and changing your body chemistry (by applying ice water to the face, intensely exercising, pacing your breathing, and progressively relaxing muscles). Each of these strategies was explained to the participant and, when appropriate, practiced during the appointment.	NR	NR

Abbreviations: BPD = bipolar disorder; CBT = cognitive behavioral therapy; DBT = dialectical behavioral therapy; IG = intervention group; NR = not reported; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor.

Appendix G Table 5. Results for Suicide Deaths, Suicide Attempts, and All-Cause Mortality Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Measure	IG	Analyzed	FUP, wks	OR (95% CI)	IG n/N (%)	CG n/N (%)	p-value	Adj
Bruce, 2004[178] (O)	All-cause mortality	IG1	All	260	0.94 (0.63 to 1.41)	60/320 (18.8)	55/279 (19.7)	<0.05	Yes
	Suicide death	IG1	All	104	2.62 (0.11 to 64.45)	1/320 (0.3)	0/278 (0.0)	NR	No
Katz, 2022[185] (G)	Suicide death	IG1	All	52	3.53 (0.14 to 87.19)	1/225 (0.4)	0/264 (0.0)	NR	NR
Linehan, 2006[187] (G)	Suicide death	IG1	All	52	0.94 (0.02 to 48.44)	0/52 (0.0)	0/49 (0.0)	NA	NR
	Suicide death	IG1	All	104	0.94 (0.02 to 48.44)	0/52 (0.0)	0/49 (0.0)	NA	NR
van Spijker, 2014 (G)[198]	Suicide death	IG1	All	6	1.03 (0.02 to 52.56)	0/116 (0.0)	0/120 (0.0)	NA	NR
Borschmann, 2013[177] (G)	Self-harm	IG1	All	26	1.86 (0.53 to 6.51)	25/36 (69.4)	20/36 (55.6)	0.33	Yes
Bruce, 2004[178] (O)	Suicide attempt	IG1	All	52	0.86 (0.05 to 13.9)	1/221 (0.4)	1/191 (0.5)	NR	No
	Suicide attempt	IG1	All	104	0.64 (0.11 to 3.88)	2/183 (1.1)	3/177 (1.7)	NR	No
Davidson, 2006[181] (G)	Suicide attempt	IG1	All	52	0.77 (0.29 to 2.01)	18/48 (37.0)	21/53 (46.0)	0.59	Yes
	Suicide attempt	IG1	All	104	0.78 (0.3 to 1.98)	23/49 (43.0)	26/53 (54.0)	0.59	Yes
Goodman, 2016[183] (G)	Suicide attempt	IG1	All	26	0.56 (0.13 to 2.49)	3/46 (6.5)	5/45 (11.1)	0.487	No
Jobes, 2017[184] (G)	Suicide attempt	IG1	All	52	2.18 (0.63 to 7.6)	8/73 (11.1)	4/75 (5.3)	NR, NSD	NR
Katz, 2022[185] (G)	Suicide attempt	IG1	All	52	1.31 (0.54 to 3.13)	11/225 (4.3)	10/264 (3.8)	NR	No
Katz, 2022[185] (G)	Composite suicide behavior[FN]	IG1	All	52	1.32 (0.88 to 1.98)	65/225 (25.5)	62/264 (23.5)	0.61	Yes
Linehan, 2006[187] (G)	Suicide attempt	IG1	All	104	0.34 (0.14 to 0.8)	12/52 (23.1)	23/49 (46.7)	0.005	NR
Mühlmann, 2021 (G)[189]	Suicide attempt	IG1	All	6	1.34 (0.61 to 2.94)	15/196 (7.6)	12/206 (5.8)	NR	NR

Appendix G Table 5. Results for Suicide Deaths, Suicide Attempts, and All-Cause Mortality Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Measure	IG	Analyzed	FUP, wks	OR (95% CI)	IG n/N (%)	CG n/N (%)	p-value	Adj
	Suicide attempt	IG1	All	32	1.06 (0.57 to 1.98)	22/196 (11.2)	22/206 (10.7)	NR	NR
Pistorello, 2012[191] (G)	Suicide attempt	IG1	All	13	4.59 (0.48 to 43.63)	4/31 (11.5)	1/32 (3.2)	NR	NR
	Suicide attempt	IG1	All	26	1.03 (0.06 to 17.28)	1/31 (4.5)	1/32 (4.0)	NR	NR
	Suicide attempt	IG1	All	39	1.03 (0.02 to 53.61)	0/31 (0.0)	0/32 (0.0)	NR	NR
	Suicide attempt	IG1	All	52	1.03 (0.02 to 53.61)	0/31 (0.0)	0/32 (0.0)	NR	NR
	Suicide attempt	IG1	All	78	0.5 (0.04 to 5.81)	1/31 (4.3)	2/32 (7.1)	NR	NR
Riblet, 2022[194] (G)	Suicide attempt	IG1	All	13	1 (0.02 to 55.27)	0/10 (0.0)	0/10 (0.0)	NR	NR
Simon, 2022[195] (G)	Self-harm	IG1	All	78	1.06 (0.85 to 1.31)	172/6230 (3.3)	162/6187 (3.1)	0.52	NR
	Self-harm	IG2	All	78	1.27 (1.03 to 1.57)	206/6227 (3.9)	162/6187 (3.1)	0.015	NR
	Self-harm, severe	IG1	All	78	(to)	NR/6230 (NR)	NR/6187 (NR)	0.84	NR
	Self-harm, severe	IG2	All	78	(to)	NR/6227 (NR)	NR/6187 (NR)	0.07	NR
van Spijker, 2014 (G)[198]	Suicide attempt	IG1	All	6	0.58 (0.16 to 2.02)	4/116 (3.4)	7/120 (5.8)	0.351	NR
Ward-Ciesielski, 2017[199] (G)	Suicide attempt	IG1	All	12	1.02 (0.2 to 5.35)	3/46 (6.5)	3/47 (6.4)	NR, NSD	NR

[FN] Suicide-related events: Nonfatal suicide attempt, interrupted attempt, death by suicide, or hospitalization to prevent suicide.

Abbreviations: Adj = adjusted; CG = control group; CI = confidence interval; FUP = followup; IG = intervention group; NA = not applicable; NR = not reported; NSD = no significant difference; OR = odds ratio.

Appendix G Table 6. Results for Suicidal Ideation and Other Continuous Suicide-Related Measures Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Kovac, 2002[186] (G)	ASIQ	0-150	Worse	All	IG1	2	25	24	28.9 (20.5)	28 (16.6)	-4.2 (19.3)	-1.6 (16.1)	-2.5 (-12.5 to 7.4)	NSD	NR
	ASIQ	0-150	Worse	All	IG1	6	25	24	28.9 (20.5)	28 (16.6)	-0.7 (20.8)	-4.4 (15.8)	3.6 (-6.7 to 14)	NSD	NR
Mühlmann, 2021[189] (G)	BHS	0-20	Worse	All	IG1	6	196	206	15.1 (3.9)	15.1 (4.2)	-3.6 (5.3)	-1.5 (5.1)	-2 (-3 to -1)	<0.0001	Yes
	BHS	0-20	Worse	All	IG1	32	196	206	15.1 (3.9)	15.1 (4.2)	-5.5 (5.7)	-3.8 (5.5)	-1.3 (-3.7 to -0.1)	0.0277	Yes
Pistorello, 2021[192] (G)	BHS	0-20	Worse	All	IG1	13	29	22	12.8 (4.8)	13 (5)	-6 (5.2)	-5.4 (5.2)	-0.6 (-3.5 to 2.3)	0.79	
Riblet, 2022[194] (G)	BHS	0-20	Worse	All	IG1	4	10	10	6.6 (9.8)	6.5 (5.6)	-3.5 (12.3)	-2.8 (7.1)	-0.7 (-9.5 to 8.1)	NSD	NR
	BHS	0-20	Worse	All	IG1	13	10	10	6.6 (9.8)	6.5 (5.6)	-4.3 (12.4)	-1.8 (7.1)	-2.5 (-11.3 to 6.3)	NSD	NR
van Spijker, 2014[198] (G)	BHS	0-20	Worse	All	IG1	6	116	120	14.7 (3.5)	14.1 (3.9)	-1.9 (4.9)	-0.7 (3.6)	-1.2 (-2.3 to -0.1)	0.029	NR
Bush, 2017[179] (G)	BSS	0-10	Worse	All	IG1	3	58	60	3.3 (2.6)	3.6 (2.8)	0.1 (2.6)	-0.2 (2.8)	0.4 (-0.6 to 1.3)	NSD	Yes
Bush, 2017[179] (G)	BSS	0-10	Worse	All	IG1	6	58	60	3.3 (2.6)	3.6 (2.8)	-0.4 (2.6)	-0.6 (2.8)	0.2 (-0.8 to 1.2)	NSD	Yes
Bush, 2017[179] (G)	BSS	0-10	Worse	All	IG1	12	58	60	3.3 (2.6)	3.6 (2.8)	-0.1 (2.7)	-0.4 (2.8)	0.2 (-0.7 to 1.2)	NSD	Yes
Goodman, 2016[183] (G)	BSS	0-38	Worse	All	IG1	13	46	45	12 (9.6)	12.6 (9.2)	-2.2 (NR)	-0.6 (NR)	NR	NR	Yes

Appendix G Table 6. Results for Suicidal Ideation and Other Continuous Suicide-Related Measures Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
	BSS	0-38	Worse	All	IG1	26	46	45	12 (9.6)	12.6 (9.2)	-1.8 (NR)	-3.2 (NR)	NR	NR	Yes
Mühlmann, 2021 (G)[189]	BSS	0-38	Worse	All	IG1	6	196	206	19.1 (6.6)	18.7 (6)	-8.5 (8.6)	-5.8 (8.2)	-2.9 (-4.5 to -1.3)	0.0005	Yes
	BSS	0-38	Worse	All	IG1	32	196	206	19.1 (6.6)	18.7 (6)	-9.6 (8.3)	-8 (8.3)	-2 (-3.7 to -0.2)	0.0295	Yes
Riblet, 2022[194] (G)	BSS	0-38	Worse	All	IG1	4	10	10	4.6 (11.7)	3.3 (6.7)	-3.4 (15.7)	-1.3 (9.1)	-2.1 (-13.3 to 9.1)	NSD	NR
	BSS	0-38	Worse	All	IG1	13	10	10	4.6 (11.7)	3.3 (6.7)	-3.9 (15.7)	0.2 (9.1)	-4.1 (-15.4 to 7.2)	NSD	NR
van Spijker, 2014 (G)[198]	BSS	0-38	Worse	All	IG1	6	116	120	15.2 (6.8)	14.5 (7.3)	-4.5 (8.7)	-2.3 (6.6)	-2.2 (-4.1 to -0.2)	0.036	NR
Pigeon, 2019[190] (G)	C-SSRS	0-25	Worse	All	IG1	6	24	26	13 (3.6)	12 (2.6)	-6.9 (5.9)	-4.2 (5.5)	-2.7 (-5.9 to 0.4)	NR	Yes
Franklin, 2016[182] (G)	Days w/ suicidal ideation	NA	Worse	All	IG1	4	51	58	11.7 (13.9)	9.1 (12.9)	-6.1 (12.2)	-4.3 (11.3)	-1.8 (-6.2 to 2.6)	NR, NSD	No
Van Orden, 2021 (O)[197]	GSIS	NR	Worse	All	IG1	3	30	27	7.8 (3.3)	7.8 (3.1)	NR	NR	-0.6 (-1.6 to 0.4)	0.257	Yes
	GSIS	NR	Worse	All	IG1	6	30	27	7.8 (3.3)	7.8 (3.1)	NR	NR	-0.3 (-1.3 to 0.7)	0.609	Yes
	GSIS	NR	Worse	All	IG1	10	30	27	7.8 (3.3)	7.8 (3.1)	NR	NR	-0.3 (-1.4 to 0.7)	0.511	Yes
Linehan, 2006[187] (G)	SBQ	3-18	Worse	All	IG1	52	52	49	51.7 (20.3)	59.9 (21.6)	-21.9 (22.7)	-27.1 (24.3)	5.2 (-4 to 14.4)	0.31	NR

Appendix G Table 6. Results for Suicidal Ideation and Other Continuous Suicide-Related Measures Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
	SBQ	3-18	Worse	All	IG1	104	52	49	51.7 (20.3)	59.9 (21.6)	-27.6 (20.1)	-28 (24.6)	0.4 (-8.4 to 9.1)	0.31	NR
Pistorello, 2012[191] (G)	SBQ	0-88	Worse	All	IG1	13	31	32	31.4 (14.6)	32.9 (18.3)	-6.1 (17.4)	-5.3 (18.6)	-0.7 (-9.6 to 8.2)	NR, NSD	No
	SBQ	0-88	Worse	All	IG1	26	31	32	31.4 (14.6)	32.9 (18.3)	-8.1 (16.9)	-9 (18)	1 (-7.7 to 9.6)	NR, NSD	No
	SBQ	0-88	Worse	All	IG1	39	31	32	31.4 (14.6)	32.9 (18.3)	-14.2 (14.7)	-5.5 (20.7)	-8.7 (-17.6 to 0.2)	NR, NSD	No
	SBQ	0-88	Worse	All	IG1	52	31	32	31.4 (14.6)	32.9 (18.3)	-17.8 (13.6)	-8 (19.3)	-9.8 (-18.1 to -1.5)	<0.05	No
	SBQ	0-88	Worse	All	IG1	78	31	32	31.4 (14.6)	32.9 (18.3)	-20.8 (13)	-9 (20.9)	-11.8 (-20.4 to -3.1)	<0.05	No
Torok, 2022[196] (G)	SIDAS	0-50	Worse	All	IG1	6	228	227	22.9 (7.9)	22.4 (8.5)	-7.9 (9.4)	-3.1 (8.8)	-4.9 (-7.6 to -2.2)	<0.001	No
Pistorello, 2021[192] (G)	SSI	0-38	Worse	All	IG1	13	29	22	13.8 (5.1)	13.7 (7.1)	-8.1 (5.9)	-6.4 (6.8)	-1.8 (-5.2 to 1.7)	0.83	NR
Ward-Ciesielski, 2017[199] (G)	SSI	0-38	Worse	All	IG1	1	34	37	19.8 (5.2)	18.6 (5.4)	-7 (6.5)	-6.6 (7.6)	-0.4 (-3.8 to 2.9)	NR, NSD	NR
	SSI	0-38	Worse	All	IG1	4	35	35	19.8 (5.2)	18.6 (5.4)	-8.4 (6.9)	-7.7 (7.6)	-0.7 (-4.1 to 2.7)	NR, NSD	NR
	SSI	0-38	Worse	All	IG1	12	39	30	19.8 (5.2)	18.6 (5.4)	-9.2 (7.7)	-10.2 (7.7)	1 (-2.7 to 4.7)	NR, NSD	NR
Priebe, 2012[193] (G)	Days w/ self-harm	0-30	Worse	All	IG1	8	38	36	14.7 (20.3)	13 (16.3)	-2.4 (NR)	-3.7 (NR)	NR	<0.001	No

Appendix G Table 6. Results for Suicidal Ideation and Other Continuous Suicide-Related Measures Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
	Days w/ self-harm	0-30	Worse	All	IG1	17	38	36	14.7 (20.3)	13 (16.3)	-9.6 (NR)	-0.1 (NR)	NR	<0.001	No
	Days w/ self-harm	0-30	Worse	All	IG1	26	38	36	14.7 (20.3)	13 (16.3)	-10.6 (NR)	-6.1 (NR)	NR	<0.001	No
	Days w/ self-harm	0-30	Worse	All	IG1	35	38	36	14.7 (20.3)	13 (16.3)	-10.5 (NR)	-2.4 (NR)	NR	<0.001	No
	Days w/ self-harm	0-30	Worse	All	IG1	43	38	36	14.7 (20.3)	13 (16.3)	-7 (NR)	-1.3 (NR)	NR	<0.001	No
	Days w/ self-harm	0-30	Worse	All	IG1	52	38	36	14.7 (20.3)	13 (16.3)	-9.9 (NR)	0.5 (NR)	NR	<0.001	No
Carter, 2010[180] (G)	Self-harm episodes	NA	NA	All	IG1	13	18	23	22 (28.6)	18.1 (40.7)	-16.3 (24.9)	-11.9 (36.3)	-4.3 (-24 to 15.3)	NR	NR
Carter, 2010[180] (G)	Self-harm episodes	NA	NA	All	IG1	26	18	23	22 (28.6)	18.1 (40.7)	-16.7 (25.6)	-8.9 (36.9)	-7.9 (-27.9 to 12.1)	NR	NR
Davidson, 2006[181] (G)	Self-harm episodes	NA	Worse	All	IG1	52	52	47	NR	NR	FU=35 (91)	FU=27 (64)	9 (-18 to 36)	0.51	Yes
	Self-harm episodes	NA	Worse	All	IG1	104	53	48	NR	NR	FU=50 (136)	FU=38 (89)	16 (-24 to 56)	0.44	Yes
McMain, 2017[188] (G)	Suicide attempts and self-injury episodes	NA	NA	All	IG1	10	42	42	9.1 (8.3)	8.3 (7.6)	-4 (7.2)	-2.6 (6.7)	-1.4 (-4.4 to 1.5)	NR	NR
	Suicide attempts	NA	NA	All	IG1	20	42	42	9.1 (8.3)	8.3 (7.6)	-6.2 (7.4)	-4.4 (6.6)	-1.9 (-4.9 to	0.30	NR

Appendix G Table 6. Results for Suicidal Ideation and Other Continuous Suicide-Related Measures Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
	and self-injury episodes												1.2)		
	Suicide attempts and self-injury episodes	NA	NA	All	IG1	32	42	42	9.1 (8.3)	8.3 (7.6)	-7.7 (7.7)	-5.8 (6.7)	-1.9 (-5 to 1.2)	0.04	NR

Abbreviations: Adj = adjusted; ASIQ = Adult Suicidal Ideation Questionnaire; BL = baseline; BHS = Beck Hopelessness Scale; BSS = Beck Scale for Suicide Ideation; CG = control group; Chg = change; CI = confidence interval; C-SSRS = Columbia-Suicide Severity Rating Scale; Diff = difference; FUP = followup; GSIS = Geriatric Suicide Ideation Scale; IG = intervention group; NA = not applicable; NSD = no significant difference; NR = not reported; SBQ = Suicide Behaviors Questionnaire; SD = standard deviation; SIDAS = Suicidal Ideation Attributes Scale; SSI = suicidal ideation.

Appendix G Table 7. Results for Depression Measures Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Goodman, 2016[183] (G)	BDI	0-63	Worse	All	IG1	13	46	45	26.1 (10.9)	31.4 (10.7)	-1.7 (NR)	-4 (NR)	NR	NR	Yes
	BDI	0-63	Worse	All	IG1	26	46	45	26.1 (10.9)	31.4 (10.7)	-4.6 (NR)	-10 (NR)	NR	NR	Yes
Davidson, 2006[181] (G)	BDI-II	0-63	Worse	All	IG1	52	52	47	NR	NR	FU=29.6 (14.8)	FU=31.3 (16.6)	-1.9 (-7.8 to 4.1)	0.54	Yes
	BDI-II	0-63	Worse	All	IG1	104	53	48	NR	NR	FU=26.5 (15.3)	FU=28.8 (15.7)	-3.2 (-9.8 to 3.4)	0.34	Yes
McMain, 2017[188] (G)	BDI-II	0-63	Worse	All	IG1	10	42	42	32.7 (10.9)	36.7 (11.5)	-5 (10.3)	-3.5 (11.2)	-1.5 (-6.1 to 3.1)	NR	Yes
	BDI-II	0-63	Worse	All	IG1	20	42	42	32.7 (10.9)	36.7 (11.5)	-9.9 (11.8)	-7 (12.6)	-2.9 (-8.2 to 2.3)	0.08	Yes
	BDI-II	0-63	Worse	All	IG1	32	42	42	32.7 (10.9)	36.7 (11.5)	-4.7 (14.2)	-7.2 (14.1)	2.5 (-3.6 to 8.5)	0.62	Yes
Pistorello, 2012[191] (G)	BDI-II	0-63	Worse	All	IG1	13	31	32	34.7 (8.7)	30.6 (11.4)	-15.8 (11)	-10.3 (11.9)	-5.5 (-11.2 to 0.1)	NR, NSD	No
	BDI-II	0-63	Worse	All	IG1	26	31	32	34.7 (8.7)	30.6 (11.4)	-15.8 (8.9)	-9.9 (14)	-5.9 (-11.7 to -0.1)	NR, NSD	No
	BDI-II	0-63	Worse	All	IG1	39	31	32	34.7 (8.7)	30.6 (11.4)	-21.7 (9.6)	-8.9 (14.9)	-12.8 (-19 to -6.6)	<0.05	No
	BDI-II	0-63	Worse	All	IG1	52	31	32	34.7 (8.7)	30.6 (11.4)	-25.9 (8.6)	-13.9 (12.2)	-12 (-17.2 to -6.7)	<0.01	No
	BDI-II	0-63	Worse	All	IG1	78	31	32	34.7 (8.7)	30.6 (11.4)	-27.1 (8.3)	-15.2 (13.3)	-12 (-17.4 to -6.5)	<0.01	No

Appendix G Table 7. Results for Depression Measures Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
van Spijker, 2014 (G)[198]	BDI-II	0-63	Worse	All	IG1	6	116	120	27.6 (9.3)	26.5 (9)	-3.9 (10.1)	-1.8 (8.8)	-2.1 (-4.5 to 0.3)	0.086	NR
Borschmann, 2013[177] (G)	HADS-D	0-21	Worse	All	IG1	26	35	34	11.8 (5)	11.8 (4.3)	-1.6 (5)	-1.3 (4)	-0.3 (-2.4 to 1.8)	NR	NR
Bruce, 2004[178] (O)	HAM-D	0-52	Worse	All	IG1	17	320	278	18.6 (6.1)	17.5 (5.8)	-7.4 (6.9)	-3.9 (7.5)	-3.5 (-4.7 to -2.3)	<0.001	Yes
	HAM-D	0-52	Worse	All	IG1	35	320	278	18.6 (6.1)	17.5 (5.8)	-8.2 (6.8)	-6.2 (6.8)	-2.1 (-3.4 to -0.9)	<0.001	Yes
	HAM-D	0-52	Worse	All	IG1	52	320	278	18.6 (6.1)	17.5 (5.8)	-8.8 (6.8)	-7.2 (6.3)	-1.8 (-3.1 to -0.5)	0.006	Yes
	HAM-D	0-52	Worse	All	IG1	78	320	278	18.6 (6.1)	17.5 (5.8)	-8.9 (7.2)	-7.8 (6.4)	-1.3 (-2.6 to 0)	0.06	Yes
	HAM-D	0-52	Worse	All	IG1	104	320	278	18.6 (6.1)	17.5 (5.8)	-9.8 (6.9)	-8.3 (6.2)	-1.9 (-3.2 to -0.5)	0.007	Yes
Linehan, 2006[187] (G)	HAM-D	0-52	Worse	All	IG1	52	52	49	20.2 (5.9)	21.7 (7.3)	-6.2 (6.7)	-4.7 (7.8)	-1.5 (-4.3 to 1.3)	0.43	NR
	HAM-D	0-52	Worse	All	IG1	104	52	49	20.2 (5.9)	21.7 (7.3)	-7.6 (6.4)	-7.3 (8.3)	-0.3 (-3.2 to 2.6)	0.43	NR
Mühlmann, 2021 (G)[189]	HAM-D	0-52	Worse	All	IG1	6	196	206	13.6 (4.1)	12.7 (4.3)	-4.4 (5.3)	-2.7 (5.3)	-1.3 (-2.3 to 0)	0.054	Yes
	HAM-D	0-52	Worse	All	IG1	32	196	206	13.6 (4.1)	12.7 (4.3)	-5.2 (5.1)	-4.3 (5.3)	-0.1 (-1.3 to 1.2)	0.3985	Yes

Appendix G Table 7. Results for Depression Measures Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Pigeon, 2019[190] (G)	PHQ-9	0-27	Worse	All	IG1	6	24	26	15.6 (5.1)	16.3 (5.5)	-9 (4.9)	-3.9 (5.3)	-5.1 (-8 to -2.3)	NR	Yes
Torok, 2022[196] (G)	PHQ-9	0-27	Worse	All	IG1	6	228	227	17.1 (5.6)	17.2 (5.7)	-4.1 (6.1)	-3.1 (6.1)	-0.9 (-2.2 to 0.3)	0.135	No
Ward-Ciesielski, 2017[199] (G)	PHQ-9	0-27	Worse	All	IG1	1	41	39	16.4 (6.2)	17.3 (5.7)	-3 (6.8)	-2.9 (6.1)	-0.1 (-3 to 2.7)	NR, NSD	NR
	PHQ-9	0-27	Worse	All	IG1	4	36	38	16.4 (6.2)	17.3 (5.7)	-3.2 (6.2)	-3.8 (6.3)	0.6 (-2.3 to 3.4)	NR, NSD	NR
	PHQ-9	0-27	Worse	All	IG1	12	39	31	16.4 (6.2)	17.3 (5.7)	-3.7 (6.5)	-4.2 (6.5)	0.5 (-2.6 to 3.5)	NR, NSD	NR
Van Orden, 2021 (O)[197]	QIDS	0-27	Worse	Older adults	IG1	3	30	27	8.4 (4.3)	7.4 (5.3)	NR	NR	-3.2 (-4.9 to -1.4)	0.000	Yes
	QIDS	0-27	Worse	Older adults	IG1	6	30	27	8.4 (4.3)	7.4 (5.3)	NR	NR	-2.2 (-3.9 to -0.5)	0.012	Yes
	QIDS	0-27	Worse	Older adults	IG1	10	30	27	8.4 (4.3)	7.4 (5.3)	NR	NR	-2.5 (-4.1 to -0.8)	0.014	Yes
Kovac, 2002[186] (G)	ZSDS	20-80	Worse	All	IG1	2	25	24	44.1 (9.3)	42.5 (8.7)	-1.1 (9.9)	-1.1 (8.1)	0 (-5.1 to 5)	NSD	NR
	ZSDS	20-80	Worse	All	IG1	6	25	24	44.1 (9.3)	42.5 (8.7)	-2.9 (10.2)	-1.2 (8.9)	-1.8 (-7.1 to 3.6)	NSD	NR

Abbreviations: Adj = adjusted; BDI = Beck Depression Inventory; BL = baseline; CG = control group; Chg = change; CI = confidence interval; Diff = difference; FUP = followup; HADS-D = Hospital Anxiety and Depression Scale – Depression; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; NR = not reported; NSD = no significant difference; PHQ = Patient Health Questionnaire; QIDS = Quick Inventory of Depressive Symptoms; SD = standard deviation; ZSDS = Zung Self-Rating Depression Scale.

Appendix G Table 8. Results for Other Mental Health Outcomes Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Goodman, 2016[183] (G)	Anxiety symptoms	BAI	0-63	Worse	All	IG1	13	46	45	24.9 (13.4)	27 (13.3)	-3.8 (NR)	-1.7 (NR)	NR	NR	Yes
	Anxiety symptoms	BAI	0-63	Worse	All	IG1	26	46	45	24.9 (13.4)	27 (13.3)	-8.4 (NR)	-6.2 (NR)	NR	NR	Yes
Ward-Ciesielski, 2017[199] (G)	Anxiety symptoms	BAI	0-63	Worse	All	IG1	1	41	39	12.8 (10.1)	14.3 (9.5)	-5.5 (9.2)	-6.1 (9.2)	0.7 (-3.4 to 4.7)	NR, NSD	NR
	Anxiety symptoms	BAI	0-63	Worse	All	IG1	4	36	38	12.8 (10.1)	14.3 (9.5)	-4.6 (9.5)	-5.8 (9.3)	1.2 (-3.1 to 5.5)	NR, NSD	NR
	Anxiety symptoms	BAI	0-63	Worse	All	IG1	12	39	31	12.8 (10.1)	14.3 (9.5)	-5.6 (9.2)	-5.8 (9.5)	0.2 (-4.2 to 4.6)	NR, NSD	NR
Torok, 2022[196] (G)	Anxiety symptoms	GAD-7	0-21	Worse	All	IG1	6	228	227	12.6 (5)	12 (5.2)	-2.8 (4.9)	-1.5 (5.3)	-0.9 (-1.9 to 0.1)	0.069	No
Borschmann, 2013[177] (G)	Anxiety symptoms	HADS-A	0-21	Worse	All	IG1	26	37	36	14.5 (4.1)	14.5 (5.6)	0.1 (4)	-1.5 (5.1)	1.6 (-0.4 to 3.7)	NR	NR
van Spijker, 2014 (G)[198]	Anxiety symptoms	HADS-A	0-21	Worse	All	IG1	6	116	120	10.6 (3.5)	10.1 (3.9)	-1 (3.9)	-0.5 (3.3)	-0.5 (-1.4 to 0.4)	0.270	10.6 (3.5)
Davidson, 2006[181] (G)	Anxiety symptoms	STAI-S	20-80	Worse	All	IG1	52	52	47	NR	NR	FU=49.2 (14.8)	FU=49.7 (15.5)	-2.7 (-8.5 to 3.2)	0.36	Yes
	Anxiety symptoms	STAI-S	20-80	Worse	All	IG1	104	53	48	NR	NR	FU=48.2 (14.4)	FU=50.9 (15.7)	8 (-14.2 to 1.7)	0.013	Yes
	Anxiety symptoms	STAI-T	20-80	Worse	All	IG1	52	52	47	NR	NR	FU=59.7 (10.3)	FU=60 (11.2)	-1.7 (-6.2 to 2.7)	0.44	Yes
	Anxiety symptoms	STAI-T	20-80	Worse	All	IG1	104	52	47	NR	NR	FU=56.4 (11.9)	FU=58 (10.9)	-4.1 (-8.8 to 0.6)	0.089	Yes
Priebe, 2012[193] (G)	Global mental health symptoms	BPRS	24-168	Worse	All	IG1	52	40	34	50 (5.6)	52.8 (9.9)	-2 (10.1)	-1.8 (10.4)	-0.2 (-4.9 to 4.5)	0.38	NR
	Global mental health symptoms	BSI	0-212	Worse	All	IG1	52	29	31	122 (41.2)	134 (39.3)	-21.4 (51)	-18 (47.2)	-3.4 (-28.2 to 21.4)	0.77	NR

Appendix G Table 8. Results for Other Mental Health Outcomes Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
Davidson, 2006[181] (G)	Global mental health symptoms	BSI-GSI	33-81	Worse	All	IG1	52	52	47	NR	NR	FU=2 (0.9)	FU=2 (0.9)	-0.3 (-0.6 to 0.1)	0.11	Yes
	Global mental health symptoms	BSI-GSI	33-81	Worse	All	IG1	104	52	47	NR	NR	FU=1.8 (1)	FU=1.9 (1)	-0.3 (-0.7 to 0.1)	0.10	Yes
Jobes, 2017[184] (G)	Global mental health symptoms	OQ-45	0-180	Worse	All	IG1	4	71	71	96.1 (19)	99 (23.4)	-15.7 (23.8)	-15.7 (29.3)	0 (-8.8 to 8.8)	NR, NSD	NR
	Global mental health symptoms	OQ-45	0-180	Worse	All	IG1	13	67	67	96.1 (19)	99 (23.4)	-23.2 (20.9)	-18.8 (29.7)	-4.4 (-13.1 to 4.3)	NR, NSD	NR
	Global mental health symptoms	OQ-45	0-180	Worse	All	IG1	26	62	64	96.1 (19)	99 (23.4)	-23.7 (25)	-22.7 (30.3)	-1 (-10.7 to 8.7)	NR, NSD	NR
	Global mental health symptoms	OQ-45	0-180	Worse	All	IG1	52	57	58	96.1 (19)	99 (23.4)	-26.1 (32.2)	-26.8 (31.2)	0.7 (-10.9 to 12.3)	NR, NSD	NR
McMain, 2017[188] (G)	Global mental health symptoms	SCL-90R	NR	Worse	All	IG1	10	42	42	2 (0.6)	2.1 (0.7)	-0.3 (0.6)	-0.1 (0.7)	-0.2 (-0.5 to 0.1)	NR	Yes
	Global mental health symptoms	SCL-90R	NR	Worse	All	IG1	20	42	42	2 (0.6)	2.1 (0.7)	-0.7 (0.6)	-0.3 (0.7)	-0.4 (-0.7 to -0.1)	0.005	Yes
	Global mental	SCL-90R	NR	Worse	All	IG1	32	42	42	2 (0.6)	2.1 (0.7)	-0.5 (0.7)	-0.4 (0.8)	-0.1 (-0.4 to 0.2)	0.50	Yes

Appendix G Table 8. Results for Other Mental Health Outcomes Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
	health symptoms															
Borschmann, 2013[177] (G)	Global mental health symptoms	WEMWBS	14-70	Better	All	IG1	26	36	35	29.6 (11.1)	31.7 (10.1)	4.7 (11.2)	3.5 (10.2)	1.2 (-3.8 to 6.2)	NR	NR
McMain, 2017[188] (G)	Other mental health	BIS-II	NR	Worse	All	IG1	10	42	42	57.8 (9)	55.8 (10)	-2.5 (8.4)	0.2 (9)	-2.7 (-6.4 to 1)	NR	Yes
	Other mental health	BIS-II	NR	Worse	All	IG1	20	42	42	57.8 (9)	55.8 (10)	-5 (9.4)	0.4 (9.3)	-5.4 (-9.4 to -1.4)	0.52	Yes
	Other mental health	BIS-II	NR	Worse	All	IG1	32	42	42	57.8 (9)	55.8 (10)	-4.5 (10.4)	-0.7 (9.6)	-3.8 (-8.1 to 0.4)	0.90	Yes
	Other mental health	BSL	NR	Worse	All	IG1	10	42	42	56.3 (16.5)	58.8 (19.6)	-11.3 (15.3)	-5.1 (18.7)	-6.2 (-13.5 to 1.1)	NR	Yes
	Other mental health	BSL	NR	Worse	All	IG1	20	42	42	56.3 (16.5)	58.8 (19.6)	-22.6 (17.7)	-10.3 (21)	-12.4 (-20.7 to -4)	0.01	Yes
	Other mental health	BSL	NR	Worse	All	IG1	32	42	42	56.3 (16.5)	58.8 (19.6)	-15.3 (20.1)	-12.8 (23.7)	-2.5 (-11.9 to 6.9)	0.77	Yes
	Other mental health	DERS	36-180	Worse	All	IG1	10	42	42	131.4 (17.8)	132.8 (16.8)	-12.4 (16.8)	-3.1 (16.3)	-9.4 (-16.5 to -2.3)	NR	Yes
	Other mental health	DERS	36-180	Worse	All	IG1	20	42	42	131.4 (17.8)	132.8 (16.8)	-24.9 (19.1)	-6.1 (17.9)	-18.8 (-26.7 to -10.9)	0.001	Yes
	Other mental health	DERS	36-180	Worse	All	IG1	32	42	42	131.4 (17.8)	132.8 (16.8)	-20.8 (23.7)	-4.7 (19.2)	-16.1 (-25.3 to -6.8)	0.01	Yes

Appendix G Table 8. Results for Other Mental Health Outcomes Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
McMain, 2017[188] continued (G)	Other mental health	DTS	NR	Worse	All	IG1	10	42	42	5.1 (2.5)	4.4 (2.3)	1.3 (2.3)	0.5 (2.1)	0.8 (-0.1 to 1.8)	NR	Yes
	Other mental health	DTS	NR	Worse	All	IG1	20	42	42	5.1 (2.5)	4.4 (2.3)	2.7 (2.7)	1 (2.4)	1.7 (0.6 to 2.8)	0.005	Yes
	Other mental health	DTS	NR	Worse	All	IG1	32	42	42	5.1 (2.5)	4.4 (2.3)	2.7 (3.2)	0.8 (2.6)	1.9 (0.6 to 3.1)	0.005	Yes
	Other mental health	STAXI	NR	Worse	All	IG1	10	42	42	38.7 (9.9)	45.2 (9.5)	-4.5 (9.3)	-2 (9.1)	-2.5 (-6.4 to 1.5)	NR	Yes
	Other mental health	STAXI	NR	Worse	All	IG1	20	42	42	38.7 (9.9)	45.2 (9.5)	-9 (9.6)	-4 (10.2)	-5 (-9.2 to -0.7)	0.001	Yes
	Other mental health	STAXI	NR	Worse	All	IG1	32	42	42	38.7 (9.9)	45.2 (9.5)	-8.4 (10.5)	-4.8 (11.1)	-3.6 (-8.3 to 1)	0.001	Yes

Abbreviations: Adj = adjusted; BAI = Beck Anxiety Inventory; BIS = Barratt Impulsiveness Scale; BL = baseline; BSI = Brief Symptom Inventory; BSL = Borderline Symptoms checklist; BPRS = Brief Psychiatric Rating Scale; Chg = change; CI = confidence interval; CG = control group; DERS = Difficulties in Emotion Regulation Scale; Diff = difference; DTS = Distress Tolerance Scale; FUP = followup; GAD = Generalized Anxiety Disorder scale; GSI = Global Severity Index; HADS-A = Hospital Anxiety and Depression Scale – Anxiety; IG = intervention group; NR = not reported; OQ-45 = Outcome Questionnaire 45; SCL-90R = Symptom Checklist 90 – Revised; SD = standard deviation; STAI-S = State-Trait Anxiety Inventory – State; STAI-T = State-Trait Anxiety Inventory – Trait; STAXI = State-Trait Anger Expression Inventory; WEMWBS = Warwick-Edinburgh Mental Wellbeing Scale.

Appendix G Table 9. Results for Other Health Outcomes Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
McMain, 2017[188] (G)	Functioning	SAS-SR	NR	Worse	All	IG1	10	42	42	2.8 (0.5)	2.8 (0.5)	-0.2 (0.4)	0.1 (0.5)	-0.2 (-0.5 to 0)	NR	Yes
	Functioning	SAS-SR	NR	Worse	All	IG1	20	42	42	2.8 (0.5)	2.8 (0.5)	-0.3 (0.5)	0 (0.6)	-0.4 (-0.6 to -0.1)	0.02	Yes
	Functioning	SAS-SR	NR	Worse	All	IG1	32	42	42	2.8 (0.5)	2.8 (0.5)	-0.2 (0.6)	0 (0.6)	-0.3 (-0.5 to 0)	0.19	Yes
Davidson, 2006[181] (G)	Functioning	SFQ	0-24	Worse	All	IG1	52	52	47	NR	NR	FU=13.1 (4.4)	FU=13.1 (4.6)	-0.4 (-2.2 to 142)	0.67	Yes
	Functioning	SFQ	0-24	Worse	All	IG1	104	52	47	NR	NR	FU=13 (5)	FU=12.3 (5.3)	0.1 (-1.9 to 2.1)	0.94	Yes
Borschmann, 2013[177] (G)	Functioning	WSAS	0-40	Worse	All	IG1	26	36	36	27 (6.5)	27 (7.4)	-1.2 (8)	-0.9 (7.7)	-0.3 (-3.9 to 3.3)	NR	NR
Jobes, 2017[184] (G)	Quality of Life	SF-36 MCS	0-100	Better	All	IG1	4	71	71	26 (7.8)	26.1 (8.6)	8.2 (8.4)	9.6 (10.6)	-1.4 (-4.5 to 1.7)	NR, NSD	NR
	Quality of Life	SF-36 MCS	0-100	Better	All	IG1	13	67	67	26 (7.8)	26.1 (8.6)	14.2 (17.1)	10.8 (10.6)	3.4 (-1.4 to 8.2)	NR, NSD	NR
	Quality of Life	SF-36 MCS	0-100	Better	All	IG1	26	62	64	26 (7.8)	26.1 (8.6)	14 (12.7)	13.5 (11.3)	0.5 (-3.7 to 4.7)	NR, NSD	NR
	Quality of Life	SF-36 MCS	0-100	Better	All	IG1	52	57	58	26 (7.8)	26.1 (8.6)	14.6 (11.6)	13.3 (10.2)	1.3 (-2.7 to 5.3)	NR, NSD	NR
Torok, 2022[196] (G)	Quality of Life	SWEMWBS	7-35	Better	All	IG1	6	228	227	17.1 (2.8)	17.2 (2.3)	1.4 (3)	1.1 (2.8)	0.3 (-0.3 to 0.9)	0.395	No
Van Orden, 2021[197] (O)	Quality of Life	WHOQoL-BREF	0-100	Better	Older adults	IG1	10	30	27	NR	NR	NR	NR	5.8 (1.1 to 10.5)	0.015	Yes
Carter, 2010[180] (G)	Quality of Life	WHOQoL-BREF, physical domain	0-100	Better	All	IG1	13	20	31	41.6 (16.1)	40.7 (22.4)	11.2 (18)	5.6 (21.8)	5.6 (-5.8 to 17.1)	<0.05	NR
	Quality of Life	WHOQoL-BREF, physical domain	0-100	Better	All	IG1	26	20	31	41.6 (16.1)	40.7 (22.4)	14.6 (16.9)	1.7 (21.9)	13 (1.6 to 24.3)	<0.05	NR
	Quality of Life	WHOQoL-BREF, psychological domain	0-100	Better	All	IG1	13	20	31	16.2 (14.3)	19.4 (14)	14.8 (18.8)	10.3 (19.9)	4.5 (-6.5 to 15.4)	<0.01	NR

Appendix G Table 9. Results for Other Health Outcomes Among Studies of Suicide Prevention Treatment (KQ4)

Author, Year (Pop)	Outcome	Measure	Scale range	Higher=	Analyzed	IG	FUP, wks	IG n	CG n	IG BL Mean (SD)	CG BL Mean (SD)	IG Chg Mean (SD)	CG Chg Mean (SD)	Diff in Chg (CI)	p-value	Adj
	Quality of Life	WHOQoL-BREF, psychological domain	0-100	Better	All	IG1	26	20	31	16.2 (14.3)	19.4 (14)	26.5 (16.7)	10.8 (17.5)	15.6 (5.9 to 25.3)	<0.01	NR
Van Orden, 2021 (O)[197]	Quality of Life	WHOQoL-BREF, psychological domain	0-100	Better	All	IG1	10	30	27	NR	NR	NR	NR	5.8 (1.1 to 10.5)	0.015	Yes
Davidson, 2006[181] (G)	Health status	EuroQoL	0-100	Better	All	IG1	52	52	47	NR	NR	FU=0.5 (0.4)	FU=0.6 (0.3)	-0.1 (-0.2 to 0.1)	0.31	Yes
	Health status	EuroQoL	0-100	Better	All	IG1	104	52	47	NR	NR	FU=0.6 (0.4)	FU=0.7 (0.3)	0 (-0.2 to 0.1)	0.79	Yes
van Spijker, 2014 (G)[198]	Health status	EuroQoL	0-100	Better	All	IG1	6	116	120	60 (17.8)	62.5 (18.2)	2 (19.7)	-3 (18.3)	5 (0.1 to 9.8)	0.045	NR
Borschmann, 2013[177] (G)	ED or inpt utilization	A and E attendances	NA	NA	All	IG1	26	37	36	NR	NR	FU=2.1 (5.9)	FU=1.3 (3)	NR	NR	NR
	ED or inpt utilization	Hospitalizations	NA	NA	All	IG1	26	37	36	NR	NR	FU=0.3 (1)	FU=0.2 (0.9)	NR	NR	NR
	ED or inpt utilization	Hospitalizations	NA	NA	All	IG1	26	37	36	NR	NR	FU=6.1 (12.2)	FU=4.3 (17.2)	NR	NR	NR
Carter, 2010[180] (G)	ED or inpt utilization	Hospitalizations	NA	NA	All	IG1	26	38	35	NR	NR	FU=0.5 (1.5)	FU=1.4 (4.5)	NR	NR	NR
	ED or inpt utilization	Hospitalizations	NA	NA	All	IG1	26	38	35	NR	NR	FU=0.6 (2.2)	FU=0.9 (2.6)	NR	NR	NR

Abbreviations: Adj = adjusted; BL = baseline; CG = control group; Chg = change; CI = confidence interval; Diff = difference; ED = emergency department; FUP = followup; IG = intervention group; inpt = inpatient; NA = not applicable; NR = not reported; SD = standard deviation; SAS-SR = Social Adjustment Scale–Self-Report; SF-36 MCS = Short Form 36 Mental Component Scale; SFQ = Social Functioning Questionnaire; SWEMWBS = Short Warwick Edinburgh Mental Well-Being Scale; WHOQoL-BREF = World Health Organization Quality of Life – Abbreviated; WSAS = Work and Social Adjustment Scale.

As Alves-Bradford and colleagues have declared, reducing mental health disparities, and ultimately achieving mental health equity, requires understanding the wide range of factors that influence health outcomes at multiple levels.[200] In this appendix, we have explored disparities across racial and ethnic groups in the US in screening, diagnosis, and treatment of mental health conditions, and also sought to identify potential mechanisms contributing to these disparities.

Racial and Ethnic Differences in Etiology/Risk Factors

Structural inequities that disadvantage families of color are numerous. Examples include housing policies (e.g., redlining, home loan financing), drug and criminal justice policies (e.g., treatment of crack versus powder cocaine), employment policies (e.g., exclusion of agricultural and domestic workers from unemployment and retirement benefits) and disinvestment in communities with a high proportion of Black, Hispanic, and Native American residents.[201] In addition to separating children from their parents, mass incarceration due to drug and criminal justice policies directly affect families' mental health by increasing the risk of poverty and adverse childhood experiences.[202] These factors have all contributed to wealth inequity wherein White Americans had almost 10 times the net worth of Black Americans[203] in 2016. These policies are also reflected in the healthcare system; a recent study examining capital assets of 4,476 Medicare-participating found that hospitals serving people of color had lower capital assets (-$215,121/bed, $P < .0001$) and recent purchases (-$83,608/bed, $P < .0001$). They were also less likely to offer 19 of 27 specific capital-intensive services,[204] based on data from 2013-2017.

The challenges posed by these and other structural challenges, as well as the resulting income inequality, has a damaging impact on mental health in disadvantaged communities. Income inequality is correlated with depression prevalence,[205, 206] risk of death from drug overdose,[207] and child well-being.[208] The estimated number of deaths attributable to six social factors (low education, racial segregation, low social support, individual-level poverty, income inequality, area-level poverty) in the United States is comparable to the number of deaths attributed to pathophysiological and behavioral causes.[209] While increasing awareness has led to commitments by many organizations and municipalities to mitigate inequities, the recent COVID-19 pandemic is likely to exacerbate existing inequities,[210] at least in the short term.

Although some research indicates that a strong sense of ethnic identity and job security may be protective factors among Black and Latinx Americans,[211] the interpersonal experience of racism and discrimination has a deleterious impact on mental as well as physical health. In fact, an overview of reviews found that association between discrimination and mental health to be stronger than the association with physical health.[212] In this review, discrimination was associated with higher levels of depression, anxiety symptoms, and psychological distress as well as with meeting criteria for mental health disorders. This review also found that discrimination increased the risk of health behaviors that impact mental health, including unhealthy use of alcohol and sleep disturbance.

Further, persons reporting experiences of racial discrimination were less trusting of health care workers and systems, had lower satisfaction with care, had lower ratings of patient-provider communication and relationships, lower adherence to medical recommendations, and delays in

seeking health care. For example, 32% of Black people, 20% of Latinx people, and 23% of Indigenous people report avoiding medical care because of experiences of personal discrimination due to their race or ethnicity in health care settings.[213] Similarly, a large population-based survey of older California residents found that Latinx and Asian or Pacific Islander respondents were more likely to endorse feeling uncomfortable talking to clinicians as a reason for not seeking treatment for mental health issues than White respondents.[214]

Racial and Ethnic Differences in Prevalence and Burden of Mental Health Diagnoses

According to 2008-2012 NSDUH data, multiracial adults had the highest prevalence of having a mental health condition (24.9%), followed by Native American/Alaska Native (22.7%), White (19.0%), Black (16.8%), Latinx (15.3%), and Asian/Asian-American (13.4%) adults. However, some have noted that presentation of depression can differ between Black and White Americans.[211] For example, studies have identified differences in expression of somatic and sleep symptoms, physical functioning, and psychosocial distress,[215] differences in core symptom presentation (sadness/depression vs. irritability/agitation), and differences in verbal descriptions of their mood between Black and White Americans. Thus, slightly lower prevalence could reflect some level of underdiagnosis among Black Americans. Cross-sectional NSDUH data from 2015-2019 showed that although Black, Latino, and Asian adults had lower lifetime and past-year rates of major depressive episodes (MDE) than White adults (lifetime 8.9 %, 10.2%, and 8.3% vs. 15.6%; past-year 5.4%, 5.7%, and 8.3 vs. 7.8%), Black and Latino adults had higher rates of persistence (experiencing lifetime and past-year MDE) and severity (experiencing past-year MDE with very severe impairment) compared with White adults (persistence 60.5% and 56.2% vs. 50.1%; severity 23.9% and 19.4% vs. 18.9%).[216] Thus, commonly used interview tools may not fully capture the burden of depressive disorders equally among different race and ethnic groups.

Racial and Ethnic Differences in Rates of Screening for Mental Health Conditions

We found very limited information on real-world mental health screening rates in different racial and ethnic groups. One study within an urban New England healthcare system found that, over the years 2010-2012, Latinx patients were more likely to be screened for depression (60-66% were screened) than White patients (55-59% screened), who were in turn more likely to be screened than patients who were Black (53% screened) or of Asian descent[217] (52-55% screened). A smaller but more recent study examined screening rates in a nationally representative group of 1,852 patients who had completed both the Preventive Care Self-Administered Questionnaire (PSAQ) and the MEPS Self-Administered Questionnaire in 2014-2015.[218] This study found that the percent who were assessed for depression varied by race and ethnicity, with lower rates among Hispanic (31.3% assessed), Non-Hispanic Black (38.1%), and Asian American (27.7%) respondents than among Non-Hispanic White respondents (54.4%, $p<.05$ for all males and females in all 3 race and ethnic groups).

What Is Known About the Validity of the Most Commonly Used or Recommended Instruments to Screen for Depression, Anxiety, and Suicide Risk in U.S. Racial/Ethnic Minority Patients? (Contextual Question 5)

One potential factor contributing to misdiagnosis could be the screening instruments themselves. Of particular interest for screening instruments is whether they are equally valid for all racial and ethnic groups in the United States, and therefore appropriate for population-based screening. A recent publication[219] examined the factor structure and measurement invariance of the PHQ-9 using a representative sample of over 30,000 US adults. The authors organized participants into six major groups: non-Hispanic White, non-Hispanic Black, Mexican American, other Hispanic, non-Hispanic Asian, and other/multi-racial. A two-factor structure was identified, with a cognitive/affective factor and a somatic factor. The authors further determined that the factors had the same meaning for the six major racial/ethnic groups and using the PHQ-9 to compare depression symptoms among these racial/ethnic groups was appropriate. An additional study compared the validity of the PHQ-9 among American Indian and Caucasian American patients.[220] They also determined a two-factor model was more appropriate than a single factor, and concluded it was acceptable to compare PHQ-9 scores among Caucasian American and American Indian population groups.

A smaller, older study also examined the validity of the PHQ-9 among different racial and ethnic primary care patients (n=5,053): non-Hispanic White, African American, Chinese American, and Latino.[221] They identified a single factor structure and similar mean scores for the four racial/ethnic groups. There were some minor differences between groups in the pattern of symptom endorsement. Relative to Non-Hispanic White Americans, Chinese Americans were more likely to endorse sleep changes and psychomotor symptoms and less likely to have appetite concerns. Latino participants were relatively more likely to endorse anhedonia and less likely to endorse sleep changes, appetite changes, and guilt. Item loading was very similar between Non-Hispanic White and Black participants. Despite the minor differences in symptom endorsement, the authors concluded that among the four racial/ethnic groups, the PHQ-9 measured a common concept of depression.

With respect to the other depression screening instruments, a meta-analysis of 28 studies determined that the original four-factor structure of the CES-D was not the best fit for all five racial/ethnic groups examined: African American, American Indian, Asian, White, and Hispanic.[222] This suggests that the CES-D is not measuring the same symptoms among these racial/ethnic groups. In a study looking at predictors of future MDD diagnosis, the presence of depressive symptoms based on the CES-D was a strong predictor for White participants.[223] For Black participants, however, a single-item self-rated mental health measure was a strong predictor of future MDD while CES-D score was not associated with future MDD. These associations controlled for demographic and socioeconomic variables and suggest that the CES-D may not be as accurate at capturing important aspects of depression in Black participants.

One of our included studies[48] (n=492) examined the impact of race on the measurement properties of the GDS-15 and found no difference between racial/ethnic groups (non-Hispanic

White, non-Hispanic Black, and Hispanic). However, a meta-analysis[224] with 26 studies determined that the factor structure differed when it was administered in languages other than English (Chinese, Greek, Hindi, Iranian, Italian, Japanese, Korean, Portuguese, and Turkish). A 2017 study[225] (n=2,687) also determined that while race/ethnicity (Black, Hispanic-Latina, Asian, White) did not impact the psychometric properties of the EPDS, socioeconomic status did and suggested that differences others have identified between ethnic and racial groups might be due to socioeconomic status disparities.

A study[226] from 2015 examined the cultural biases of the GAD-7 among 950 participants in the US and Canada. Participants were categorized into four racial/ethnic groups: White Americans, Hispanic, Black/African American, and White Canadians. The total score for the GAD-7 was significantly different for Black/African Americans when compared to the three other groups, but no differences were seen between the other racial and ethnic groups. Further, the original single factor structure was only a good fit for the White American group; when covariance was allowed for three items, the fit improved for all racial/ethnic groups. Further, individuals identifying as Black/African American with high GAD symptoms did not endorse three items as strongly as other racial and ethnic participants with a similar level of GAD symptoms, indicating a possible measurement bias for Black Americans. The items were Item 1 (feeling nervous, anxious, or on edge), 5 (being so restless that it is hard to sit still), and 6 (becoming easily annoyed or irritable). This same study reported a lower prevalence of GAD among Black/African American participants but suggested that it was due to a bias in the instrument rather than a true difference in GAD between racial/ethnic groups. This could mean a lower cutoff of the GAD-7 is necessary to accurately identify Black persons with anxiety symptomatology.

Racial and Ethnic Differences in Diagnosis of Mental Health Conditions

Evidence indicates that the risk of misdiagnosis is elevated for Black and Latinx Americans. Data from 1995-2005 indicated that African American and Hispanic primary care patients were less likely to be diagnosed with depression or anxiety when compared with White patients.[227] It is difficult to determine the reason for this difference in prevalence. Evidence from the 1999 National Health Interview Survey indicated that requiring a clinically significant impairment in order to receive a diagnosis of MDD led to an underestimate of depression for Black respondents.[228] However we found very limited evidence exploring reasons for lower prevalence of depression in Black patients or those in other race and ethnic groups, compared with White patients.

Examples of differences in depression presentation were described above, which may lead to underdiagnosis with a presentation considered “atypical” in that it does not present primarily with sadness or depressed mood. A study with Black and White actors simulating different depression presentations examined how licensed social workers and marriage and family therapists approached diagnosing depression.[215] This study found that diagnostic accuracy was high for both Black and White actors with a “typical” depression presentation (92-97% accuracy), but identification was lower for the “atypical” presentation (55-63% accuracy), regardless of whether the actor was Black or White. However, one study examining differential

item functioning for 20 items on the National Comorbidity Survey found that the removal of items with differential functioning between Black, Latinx, and White participants did not change the pattern of prevalence differences between the groups.[229]

Black adults have a higher rate of being diagnosed with schizophrenia,[230] a phenomena that has been documented across approximately 30 years. One group of researchers have found evidence to support a pattern of under-recognition of mood-related symptoms and over-emphasis of psychotic-spectrum symptoms, suggesting racial bias in the diagnosis of schizophrenia spectrum disorders that might also contribute to underdiagnosis of mood disorders.[231, 232] For example, in a comparison of clinical and structured interview assessments, mood symptoms identified in the structured interviews were more commonly omitted in the clinical assessments of Black patients, compared with the assessments of White patients.[232] In a separate study, Black patients were more likely to be diagnosed as having schizophrenia spectrum disorders by unblinded assessors who used structured interviews than by expert diagnosticians who used transcripts of the same interviews but who were blind to patients' race and ethnicity (i.e., race and ethnic cues were eliminated from transcripts).[231]

In a separate line of research, data from the 1990s indicated that clinicians' perception of the patient's honesty proved to be a significant predictor of racial disparities in schizophrenia diagnoses.[233] While this harmful bias may be expected to have changed over the intervening decades, unfortunately clinician bias appears to be a continuing issue. In a 2021 publication of implicit bias, medical students and psychiatrists were more likely to pair faces of Black individuals with words related to psychotic disorders (as opposed to mood disorders), non-compliance (as opposed to compliance), and antipsychotic medications (as opposed to antidepressant medications). White race and higher level of training were the strongest predictors of associating faces of Black individuals with psychotic disorders, even after adjusting for the clinician's age.[234]

Although diagnosis of children is beyond the scope of this review, another area of documented misdiagnosis is ADHD. In contrast to overdiagnosis of schizophrenia, ADHD in Black and Latinx children appear to be underdiagnosed.[235] Compared with White children and controlling for ADHD symptoms and numerous sociodemographic variables, Black children had a 60% lower odds (OR, 0.60; 95% CI, 0.27 to 0.59) and Latinx children had a 63% lower odd (OR, 0.57; 95 % CI, 0.22 to 0.60) of having received an ADHD diagnosis than White children.

Racial and Ethnic Differences in Mental Health Referral and Service Use

According to 2008-2012 NSDUH data, the rates of mental health service use are higher for US residents who are White (16.6%), multiracial (17.1%), and Native American or Alaska Native (15.6%) than people who are Black (8.6%), Latinx (7.3%) and Asian American (4.9%). There is a similar pattern across race/ethnic groups for any use of outpatient mental health services and psychotherapeutic medications. This pattern also held for men and women and across age groups and poverty status.[236]

Similarly, among persons meeting criteria for anxiety, depression, alcohol or substance use disorder, or PTSD, the Collaborative Psychiatric Epidemiologic Studies (CPES) found that White persons had the highest rates of having at least one mental health visit (35.4%), followed by Latinx (30.6%), Black (28.8%), and Asian Americans (22.9%).[237] Even controlling for the sociodemographic variables and insurance status, Asian and Black Americans had lower odds of having at least one visit compared to White Americans (OR, 0.56 [95% CI: 0.39, 0.82] and 0.74 [95% CI: 0.60, 0.92], respectively). Hispanic participants did not differ from White Americans. Asian and Black Americans had similar rates of visits to mental health practitioners in non-medical and spiritual settings that other race and ethnic groups, however.

In a group of not-for-profit healthcare systems, Asian, Black, Hispanic, Native Hawaiian or other Pacific Islander, Native American or Alaskan Native, and multiracial patients were less likely to be diagnosed with an anxiety disorder than White patients, and all of these groups except Native American or Alaskan Native patients were less likely to be diagnosed with depression. Among those with a mental health diagnosis, 77.8% of Non-Hispanic white patients received psychotropic medication, which was higher than other racial and ethnic groups (range 61.5% to 74.0%).[238] On the other hand, several racial and ethnic groups other were more likely to received psychotherapy (e.g., 33.4% among White patients, 35.7% among Black patients, 39.5% among Native American or Alaskan Native patients).

Unfortunately, the disparity in mental health treatment among people from different race and ethnic groups widened between the years 2004 and 2012.[239] Using data from a large nationally representative sample based on the Medical Expenditure Panel Surveys, the disparity widened between White respondents and Black, Latinx, and Asian American respondents in the proportion receiving any mental health care (from 8.2% to 10.8% difference between groups) and any psychotropic medication (from 7.6% to 10.0% difference). We were unable to find more recent data to determine whether this trend has continued.

Across all race and ethnic groups, cost or lack of insurance were listed as the main reason for not using mental health services, among those with a need for services.[236] Cost is an important barrier for psychiatric care because the percentage of psychiatrists who accepted Medicare is historically lower than other physicians (e.g., 54.8% vs 86.1% in 2009-2010).[240] The impact of cost hits families of color particularly hard, given the numerous federal policies that have disadvantaged Black and other people of color with respect to accumulation of wealth within and across generations. Cost and lack of insurance was followed by structural barriers for most race and ethnic groups (e.g., lacking transportation, not knowing where or how to access care). Few persons in any race and ethnic group reported low confidence that mental health services would help, but this reason was endorsed most by Asian (12.9%) and White (9.7%) respondents, followed by multiracial (7.2%), Latinx (6.5%), Black (5.3%), and Native American/Alaska Native (4.4%) respondents.[236]

Racial and Ethnic Differences in Treatment Effectiveness

Determining factors that promote success in specific populations is important. A study using the Collaborative Psychiatric Epidemiology Surveys found that Black, Latinx, and Asian American patients who were seen by a mental health specialist (vs a primary care provider) and were

prescribed medication (vs therapy alone) were more likely to remain in treatment.[241] This study found that having a mental health specialist (vs a primary care provider) resulted in the greatest impact on treatment retention. One study hints that online interventions may also help narrow gaps in treatment benefits between White and Black patients with anxiety or depression. A recent study of 2,884 patients with elevated mood and/or anxiety symptoms found the intervention to have a larger benefit for Black participants than White participants.[242] This intervention used Internet-delivered interactive sessions and "homework" assignments to complete between weekly sessions, and was supported by bachelor-level care coaches.

An overview of reviews on the effectiveness of culturally-adapted mental health interventions found that effect sizes in 12 included reviews ranged from 0.23 to 0.75, with the majority reporting moderate to large effect sizes.[243] In this review, adaptations were related to language, context, concepts, family, communication, content, cultural norms and practices, context and delivery, therapeutic alliance, and treatment goals. The reviewers noted some important limitation to this evidence, however, including a "lack of standardized frameworks for cultural adaptation of interventions that have been universally accepted, evaluated, and applied routinely in research and practice."

A recent review covering a wide range of mental health conditions identified 57 RCTs reporting an effect on symptom reduction when adapted interventions were compared to non-adapted active treatments (K = 30, Hedge's g = -0.43 [95% CI: -0.61, -0.25], p < .001).[244] In this review, organization-specific adaptations had even larger effects than therapist- or content-specific adaptations in meta-regression (p=.02); organization-specific adaptations included the format used to provide treatment (e.g., face-to-face, digital), the location of treatment (home, community, non-healthcare), the contact time and length of treatment, and method of access (accelerated access, access via alternative to standard routes).

Mitigating Inequities in Mental Health Among Race and Ethnic Groups

While increased access to care for race and ethnic minority populations is important, straightforward expansion of services as they currently exist are unlikely to eliminate inequities in mental health. A recent review proposed the following strategies (and rationales for each) to help achieve mental health equity: payment reform and increasing population-based care; delivery system reform, increasing community-based health care services; addressing the social determinants of health; engaging local communities; enhancing the pipeline of clinicians from diverse backgrounds; and supporting a diverse, structurally competent workforce.[200] Specific strategies for improving the healthcare delivery system include reducing barriers to access to care (e.g., increased availability of mental health services in geographic areas that are underserved, ease of referral from primary care settings), and increasing the use of (and training in the use of) integrated care settings. Engaging affected communities would enable the development of services that respond to patients' needs and preferences and promote flexibility in evidence-based practice.[245]

The American Psychological Association issued the following recommendations to help eliminate inequities in mental health status and mental health care through the use of

psychological and behavioral research and services that are culturally and linguistically competent:[246]

- Facilitate partnerships among physicians, mental and behavioral health providers, educators, community leaders, government agencies, and families to ensure development and implementation of culturally and linguistically competent and evidence-based prevention, early intervention, and treatment.
- Increase the availability of culturally and linguistically competent mental and behavioral health services accessible to racial and ethnic minorities.
- Increase research examining the complexities and intersections of multiple statuses/identities (e.g., socioeconomic status, disability, and immigrant status) and how these may contribute to psychological health.
- Foster positive relationships and programs within racial and ethnic minority communities to increase awareness of mental health issues and prevent environmental factors that may place individuals at risk.
- Increase funding for training mental and behavioral health professionals and to train these professionals to become culturally and linguistically competent.
- Develop and implement policy and programs based on psychological and behavioral research ensuring that racial and ethnic minorities are empowered through culturally and linguistically informed and evidence-based strategies.
- Advocate for local, State and national funding agencies to incorporate culturally and linguistically competent guidelines into proposals for programs for racial and ethnic minority children, youth, and families.
- Increase collaboration across federal funding organizations involved in racial and ethnic minority resiliency research.

Appendix I. Additional Details on Contextual Question 2: Diagnosis, Referral, and Treatment Outcomes Reported by Studies of Depression, Anxiety, or Suicide Risk Screening Studies

Author, year (Study name) Quality	Group	Pop	Outcome	Notes	FUP	IG n	CG n	IG BL	CG BL	IG mean chg (SD) or n/N (%)	CG mean chg (SD) or n/N (%)	Effect type	Between-group difference, p-value
Whooley, 2000[40] Fair	All	Older adults	Provider dx depression	Depression diagnosed by a physician	104	162	169	NR (NR)	NR (NR)	56/162 (35.0)	58/169 (34.0)	OR	1.00 (0.60 to 1.60), 0.96
Callahan, 1994[29] Fair	All	Older adults	Provider dx depression	Depression diagnosis in medical record	26	76	60	NR (NR)	NR (NR)	25/76 (32.3)	7/60 (12.1)	calc OR	3.41 (1.25 to 9.36), 0.002
Leung, 2011[33] Good	All	Perinatal	Provider dx depression	Probable depression recognized	p26	231	231	NR (NR)	NR (NR)	67/231 (29.0)	14/231 (6.0)	calc OR	6.33 (3.44 to 11.66), ≤0.05
Williams, 1999[42] Fair	Depression dx at BL	General adults	Provider dx depression	Diagnosed by physician	13	77	38	NR (NR)	NR (NR)	30/77 (39.0)	11/38 (29.0)	calc OR	1.57 (0.68 to 3.62), NSD
	MDD dx at BL	General adults	Provider dx depression	Diagnosed by physician	13	49	20	NR (NR)	NR (NR)	22/49 (45.0)	5/20 (24.0)	calc OR	2.44 (0.77 to 7.78), <0.02
Yawn, 2012[43] Fair	EPDS ≥10 at BL	Perinatal	Provider dx depression	According to PHQ-9 scores and clinician assessment (Clinician NS)	p52	322	233	NR (NR)	NR (NR)	194/322 (66.0)	78/233 (41.0)	calc OR	3.01 (2.12 to 4.28), 0.0001
Bergus, 2005[27] Fair	All	General adults	Advised counseling	-	10	24	27	NR (NR)	NR (NR)	5/24 (22.0)	3/27 (12.0)	calc OR	2.11 (0.45 to 9.95), 0.32
	PHQ-9 ≥10 at BL	General adults	Advised counseling	-	10	10	11	NR (NR)	NR (NR)	1/10 (10.0)	0/11 (0.0)	calc OR	3.63 (0.13 to 99.85), 0.28
	PHQ-9 ≥10 at BL	General adults	Advised counseling	-	10	14	16	NR (NR)	NR (NR)	4/14 (29.0)	3/16 (20.0)	calc OR	1.73 (0.31 to 9.57), 0.59
Wickberg, 2005[41] Fair	EPDS≥12 at BL	Perinatal	Referral to mental health	Study used cut-off level of 11/12 for EPDS	p10	34	31	NR (NR)	NR (NR)	13/34 (38.2)	5/31 (16.1)	calc OR	3.22 (0.99 to 10.49), NSD

Appendix I. Additional Details on Contextual Question 2: Diagnosis, Referral, and Treatment Outcomes Reported by Studies of Depression, Anxiety, or Suicide Risk Screening Studies

Author, year (Study name) Quality	Group	Pop	Outcome	Notes	FUP	IG n	CG n	IG BL	CG BL	IG mean chg (SD) or n/N (%)	CG mean chg (SD) or n/N (%)	Effect type	Between-group difference, p-value
Rost, 2001[36] Good	In treatment at BL	General adults	Referral to mental health	Referral for psychotherapy	26			NR (NR)	NR (NR)	NR (51.8)	NR (45.0)	OR	1.31 (NR), 0.32
	New treatment episode	General adults	Referral to mental health	Referral for psychotherapy	26	97	92	NR (NR)	NR (NR)	22/97 (22.7)	13/92 (14.1)	OR	1.83 (NR), 0.21
Leung, 2011[33] Good	All	Perinatal	Tx: counseling	Received counseling session	p26	231	231	NR (NR)	NR (NR)	55/231 (23.8)	11/231 (4.8)	calc OR	6.25 (3.18 to 12.30), ≤0.05
Yawn, 2012[43] Fair	EPDS ≥10 at BL	Perinatal	Tx: counseling	Tx of women with postpartum depression diagnosis	p52	322	233	NR (NR)	NR (NR)	54/322 (20.0)	20/233 (11.0)	calc OR	2.15 (1.25 to 3.70), 0.02
Wells, 2000[39] Fair	All	General adults	Any specialty counseling	-	26	770	386	NR (NR)	NR (NR)	294/770 (38.2)	99/386 (25.6)	calc OR	1.79 (1.37 to 2.35), <0.001
	All	General adults	Any specialty counseling	-	52	752	374	NR (NR)	NR (NR)	205/752 (27.3)	78/374 (20.9)	calc OR	1.42 (1.06 to 1.91), 0.03
Whooley, 2000[40] Fair	All	Older adults	Prescription for anti-depressants	-	104	162	169	NR (NR)	NR (NR)	59/162 (36.0)	72/169 (43.0)	OR	0.80 (0.50 to 1.20), 0.3
	GDS ≥11 at BL	Older adults	Prescription for anti-depressants	-	104	24	36	NR (NR)	NR (NR)	12/24 (50.0)	17/36 (47.0)	OR	1.10 (0.40 to 3.10), 0.8
Morrell, 2009[35] Fair	All	Perinatal	Antidepressant prescriptions	-	p26	1237	495	NR (NR)	NR (NR)	FUP= 0(NR)	FUP= .1(NR)	MeanDiff	-0.10 (-0.10 to 0.00), NR
	EPDS ≥12 at p06	Perinatal	Antidepressant prescriptions	-	p26	195	78	NR (NR)	NR (NR)	FUP= .3(NR)	FUP= .5(NR)	MeanDiff	-0.20 (-0.50 to 0.10), NSD
Bergus, 2005[27] Fair	All	General adults	Tx: medication	Newly prescribed AD	10	24	27	NR (NR)	NR (NR)	10/24 (42.0)	8/27 (30.0)	calc OR	1.70 (0.53 to 5.40), 0.34
	PHQ-9 ≥10 at BL	General adults	Tx: medication	Newly prescribed AD	10	14	16	NR (NR)	NR (NR)	6/14 (43.0)	7/16 (44.0)	calc OR	0.96 (0.23 to 4.10),

Appendix I. Additional Details on Contextual Question 2: Diagnosis, Referral, and Treatment Outcomes Reported by Studies of Depression, Anxiety, or Suicide Risk Screening Studies

Author, year (Study name) Quality	Group	Pop	Outcome	Notes	FUP	IG n	CG n	IG BL	CG BL	IG mean chg (SD) or n/N (%)	CG mean chg (SD) or n/N (%)	Effect type	Between-group difference, p-value
													0.96
	PHQ-9 ≥10 at BL	General adults	Tx: medication	Newly prescribed AD	10	10	11	NR (NR)	NR (NR)	4/10 (40.0)	1/11 (9.0)	calc OR	6.67 (0.60 to 74.51), 0.10
Callahan, 1994[29] Fair	All	Older adults	Tx: medication	Newly prescribed AD	26	76	60	NR (NR)	NR (NR)	20/76 (26.0)	5/60 (8.0)	calc OR	3.91 (1.21 to 12.62), 0.01
Wells, 2000[39] Fair	All	General adults	Any appropriate antidepressant meds	-	26	771	380	NR (NR)	NR (NR)	268/771 (34.7)	95/380 (25.1)	calc OR	1.60 (1.21 to 2.11), 0.001
	All	General adults	Any appropriate antidepressant meds	-	52	753	371	NR (NR)	NR (NR)	233/753 (31.0)	89/371 (24.0)	calc OR	1.42 (1.07 to 1.89), 0.01
Jarjoura, 2004[31] Fair	All	General adults	Tx: medication	-	52	33	28	NR (NR)	NR (NR)	21/33 (64.0)	4/28 (15.0)	calc OR	10.50 (2.94 to 37.54), ≤0.05
Yawn, 2012[43] Fair	EPDS ≥10 at BL	Perinatal	Tx: medication	Tx of women with postpartum depression diagnosis	p52	322	233	NR (NR)	NR (NR)	169/322 (56.0)	67/233 (35.0)	calc OR	2.74 (1.91 to 3.92), <0.0001
Rost, 2001[36] Good	In treatment at BL	General adults	Tx: medication	Received any pharmacotherapy	26			NR (NR)	NR (NR)	NR (NR)	NR (NR)		NR, NSD
	New treatment episode	General adults	Tx: medication	Received any pharmacotherapy	26	97	92	NR (NR)	NR (NR)	67/97 (69.1)	26/92 (28.3)	calc OR	5.67 (3.03 to 10.60), NSD
Jarjoura, 2004[31] Fair	All	General adults	Tx: medication or counseling	-	52	33	28	NR (NR)	NR (NR)	23/33 (70.0)	4/28 (15.0)	calc OR	13.80 (3.79 to 50.28), ≤0.05
Williams, 1999[42] Fair	MDD dx at BL	General adults	Tx: medication or counseling	-	13	49	20	NR (NR)	NR (NR)	27/49 (55.0)	6/20 (28.0)	calc OR	2.86 (0.94 to 8.69), 0.005

Appendix I. Additional Details on Contextual Question 2: Diagnosis, Referral, and Treatment Outcomes Reported by Studies of Depression, Anxiety, or Suicide Risk Screening Studies

Author, year (Study name) Quality	Group	Pop	Outcome	Notes	FUP	IG n	CG n	IG BL	CG BL	IG mean chg (SD) or n/N (%)	CG mean chg (SD) or n/N (%)	Effect type	Between-group difference, p-value
Yawn, 2012[43] Fair	EPDS ≥10 at BL	Perinatal	Tx: medication plus counseling	Tx of women with postpartum depression diagnosis	p52	322	233	NR (NR)	NR (NR)	176/322 (60.0)	70/233 (37.0)	calc OR	2.81 (1.97 to 4.01), <0.0001
Bergus, 2005[27] Fair	All	General adults	Tx: newly prescribed ADs or advised couns	-	10	24	27	NR (NR)	NR (NR)	11/24 (46.0)	9/27 (33.0)	calc OR	1.69 (0.54 to 5.26), 0.36
	PHQ-9 ≥10 at BL	General adults	Tx: newly prescribed ADs or advised couns	-	10	14	16	NR (NR)	NR (NR)	7/14 (50.0)	8/16 (50.0)	calc OR	1.00 (0.24 to 4.20), 1.0
	PHQ-9 ≥10 at BL	General adults	Tx: newly prescribed ADs or advised couns	-	10	10	11	NR (NR)	NR (NR)	4/10 (40.0)	1/11 (9.0)	calc OR	6.67 (0.60 to 74.51), 0.10
Wells, 2000[39] Fair	All	General adults	Overall appropriate care	-	26	772	380	NR (NR)	NR (NR)	393/772 (50.9)	151/380 (39.7)	calc OR	1.57 (1.23 to 2.02), <0.001
	All	General adults	Overall appropriate care	-	52	720	305	NR (NR)	NR (NR)	426/720 (59.2)	153/305 (50.1)	calc OR	1.44 (1.10 to 1.88), 0.006
Callahan, 1994[29] Fair	All	Older adults	Adequate treatment course	Remained on antidepressant for 6 mo	26	76	60	NR (NR)	NR (NR)	25/76 (33.0)	11/60 (19.0)	calc OR	2.11 (0.86 to 5.20), 0.04
Rost, 2001[36] Good	In treatment at BL	General adults	Adequate treatment-psychotherapy	≥8 session MH specialty care visits over 6 mo	26			NR (NR)	NR (NR)	NR (31.3)	NR (19.1)	OR	1.93 (NR), 0.05
	New treatment episode	General adults	Adequate treatment-psychotherapy	≥8 session MH specialty care visits over 6 mo	26	97	92	NR (NR)	NR (NR)	3/97 (3.1)	1/92 (1.1)	OR	3.48 (NR), 0.33
	In treatment at BL	General adults	Adequate treatment-pharma-cotherapy	Guideline concordant pharmacotherapy (≥3 mo at ≥minimum dose)	26			NR (NR)	NR (NR)	NR (NR)	NR (NR)		NR, NSD

Appendix I. Additional Details on Contextual Question 2: Diagnosis, Referral, and Treatment Outcomes Reported by Studies of Depression, Anxiety, or Suicide Risk Screening Studies

Author, year (Study name) Quality	Group	Pop	Outcome	Notes	FUP	IG n	CG n	IG BL	CG BL	IG mean chg (SD) or n/N (%)	CG mean chg (SD) or n/N (%)	Effect type	Between-group difference, p-value
	New treatment episode	General adults	Adequate treatment-pharma-cotherapy	Guideline concordant pharmacotherapy (≥3 mo at ≥minimum dose)	26	97	92	NR (NR)	NR (NR)	35/97 (36.1)	9/92 (9.8)	OR	5.13 (NR), <0.001

Abbreviations: AD = antidepressant; BL = baseline; CG = control group; cal = calculated; chg = change; couns = counseling; dx = diagnosis; EPDS = Edinburgh Postnatal Depression Scale; FUP = followup; GDS = Geriatric Depression Scale; IG = intervention group; MDD = major depressive disorder; MeanDiff = mean difference; MH = mental health; NR = not reported; NS = not significant; NSD = no significant difference; OR = odds ratio; PHQ = Patient Health Questionnaire; SD = standard deviation Tx =treatment.

Appendix J Table 1. Ongoing Screening Trials for Depression, Anxiety, or High Suicide Risk

Condition	Trial	Trial number	Location	N	Duration (years)	Intervention	Relevant endpoints	Estimated completion date
Depression	General Practitioner (GP) education and screening feedback for improving depression outcomes among primary care patients	ACTRN12618001139268	Australia	1992	1 year	General Practitioner education and screening feedback vs. no education and screening feedback	Proportion of patients scoring 10 or more on the Patient Health Questionnaire (PHQ-9), delivery of mental health services, supply of prescribed psychotropic medications	Dec 2021 Protocol published.
	GET.FEEDBACK.GP	NCT03988985	Germany	1074	6 months	Patient and GP-targeted feedback vs. GP-targeted feedback only vs. no feedback	Depression severity, depression treatment, quality-adjusted life years, anxiety	Sep 2022 Protocol published.
	The Efficacy of Automated Feedback After Internet-based Depression Screening (DISCOVER)	NCT04633096	Germany	1074	6 months	Tailored feedback vs. standardized feedback vs. no feedback	Depression severity, health-related quality of life, anxiety, depression diagnosis, AEs	Sep 2022 Protocol published.
	Depression Screening in Black Churches	NCT04524767	US	600	3 and 6 months	Screening, brief intervention, and referral to treatment vs. referral as	Changes in depression severity, depressive symptoms, and QoL	May 2025

Appendix J Table 1. Ongoing Screening Trials for Depression, Anxiety, or High Suicide Risk

Condition	Trial	Trial number	Location	N	Duration (years)	Intervention	Relevant endpoints	Estimated completion date
						usual or edu brochures		
Depression/Anxiety	Perinatal Identification, Referral and Integrated Management for Improving Depression: The PIRIMID Study	ACTRN12619001433190	Australia	1650	6 months	Integrated electronic screening and clinical decision support system vs. usual care	Treatment uptake, anxiety and stress symptoms, health-related quality of life	Oct 2021 No results available
	Improving mental health screening for Aboriginal and Torres Strait Islander pregnant women and mothers of young children	ACTRN12619000580178	Australia	1246	1 year	Screening with the Kimberley Mum's Mood Scale (KMMS) vs. reference standard assessment	Sensitivity of the KMMS for screening for perinatal anxiety and depression, health system responses to identified risk; pattern of change in KMMS risk	Nov 2021 Protocol Published
	New Moms Mood Tracking & Wellbeing	NCT05056454	US	200	26 weeks	Screening and Treatment of Anxiety and Depression (STAND) vs. TAU	Depression score reduction (EPDS-9), Sheehan disability scale results	June 2023
Suicide	A System of Safety (SOS)	NCT03104504	United States	31000	4.5 years	CQI initiative implementation vs. pre-initiative implementation	Standardized suicide risk screening, safety planning,	June 2023

Appendix J Table 1. Ongoing Screening Trials for Depression, Anxiety, or High Suicide Risk

Condition	Trial	Trial number	Location	N	Duration (years)	Intervention	Relevant endpoints	Estimated completion date
						(primary focus on ED, inpatient units; involvement of primary care at last phase of study)	means restriction counseling, suicide risk identification, suicide outcomes	
	Adaptive Implementation Intervention for VA Suicide Risk Identification Strategy	NCT04243330	United States	140	1 year	Audit and feedback vs. audit and feedback + external facilitation vs. implementation as usual	Columbia Suicide Severity Rating Scale Screener, comprehensive Suicide risk evaluation uptake, safety planning uptake	Apr 2023 Protocol published
	Effectiveness and Implementation of eScreening in Post 9/11 Transition Programs	NCT04506164	United States	45	NR	eScreening compared to screening as usual	Change in rate of referral to care; rate of screening completion; rate of comprehensive suicide risk evaluation	Dec 2023

Abbreviations: AE = adverse event; CQI = continuous quality improvement; ED = emergency department; edu = education; EPDS = Edinburgh Postnatal Depression Scale; GP = general practitioner; QoL = quality of life; TAU = treatment as usual.

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