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Screening for Cognitive Impairment in Older Adults: An Evidence Update for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: We conducted this systematic review to support the U.S. Preventive Services Task Force (USPSTF) in updating its recommendation on screening for cognitive impairment in older adults. Our review addresses five questions: 1) Does screening for cognitive impairment in community-dwelling older adults improve decisionmaking, patient, family/caregiver, or societal outcomes?; 2) What is the test performance of screening instruments to detect dementia or mild cognitive impairment (MCI) in community-dwelling older adult primary care patients?; 3) What are the harms of screening for cognitive impairment?; 4) Do interventions for early dementia or MCI in older adults improve decisionmaking, patient, family/caregiver, or societal outcomes?; and 5) What are the harms of interventions for cognitive impairment?

Data Sources: We reviewed 12 relevant existing systematic reviews; database searches through December 2012 in MEDLINE, PsycINFO, and the Cochrane Central Register of Controlled Trials; and additional searches for ongoing trials through ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, and Current Controlled Trials (ISRCTN Register).

Study Selection: We conducted dual independent review of 16,179 abstracts and 1,190 articles against the specified inclusion criteria, including: screening instruments that could be delivered in primary care in 10 minutes or less by a clinician or self-administered in 20 minutes or less; diagnostic accuracy studies that used a reference standard; screening studies conducted in unselected community-dwelling older adults relevant to primary care in the United States; major pharmacologic and nonpharmacologic interventions in people with MCI or mild to moderate dementia; intervention trials of efficacy; or trials and large observational studies examining adverse effects.

Data Analysis: We conducted dual independent critical appraisal of all included studies, and extracted all important study details and outcomes from fair- or good-quality studies. For diagnostic accuracy studies, we focused on sensitivity and specificity of instruments that were evaluated in more than one study. For treatment trials, we synthesized results by intervention type. We conducted a qualitative synthesis of results using summary tables and figures to capture key study characteristics, sources of clinical heterogeneity, and overall results of each study. Quantitative synthesis was limited to test performance of the Mini Mental State Examination (MMSE) (due to insufficient number of homogeneous studies for other instruments) and U.S. Food and Drug Administration (FDA)-approved medications to treat AD and other medications and dietary supplements on global cognitive outcomes; caregiver interventions on caregiver burden and depression outcomes; and nonpharmacologic interventions aimed at the patient on global cognitive outcomes.

Results: *Screening (Key Questions 1–3):* No trials examined the direct effect of screening for cognitive impairment on important patient outcomes, including patient, caregiver, and clinician decisionmaking outcomes. We identified 55 studies that addressed the diagnostic accuracy and harms of brief screening instruments to detect cognitive impairment. Most instruments were only studied in a handful of well-designed diagnostic accuracy studies in primary care—relevant populations. The MMSE remains the most thoroughly studied instrument. Pooled estimates

across 14 studies (n=10,185) resulted in 88.3 percent sensitivity (95% CI, 81.3 to 92.9) and 86.2 specificity (95% CI, 81.8 to 89.7) for a cut-point of 23/24 or 24/25 to detect dementia. Other instruments with more limited evidence to detect dementia include the Clock Drawing Test (CDT) (k=7; n=2,509), Mini-Cog (k=4; n=1,570), Memory Impairment Screen (MIS) (k=5; n=1,971), Abbreviated Mental Test (AMT) (k=4; n=824), Short Portable Mental Status Questionnaire (SPMSQ) (k=4; n=1,057), Free and Cued Selective Reminding Test (FCSRT) (k=2- n=734), 7-Minute Screen (7MS) (k=2; n=553), Telephone Interview for Cognitive Status (TICS) (k=2; n=677) and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (k=5; n=1,108). In general, these tests can have reasonable test performance, but the range of sensitivity and specificity varies across the studies likely due to clinical heterogeneity. The best-quality studies for the MIS and AMT show low sensitivity. The AMT, SPMSQ, FCRST, 7MS, and TICS have very limited evidence in English. Much more limited evidence exists for the following instruments to detect MCI: MMSE (k=15; n=5,758), IQCODE (k=4; n=975), CDT (k=4; n=4,191), Mini-Cog (k=3; n=1,092), TICS (k=3; n=568), and the Montreal Cognitive Assessment (MoCA) (k=2; n=251). The sensitivity and/or specificity of these instruments is generally worse for the detection of MCI compared with dementia. Other instruments (i.e., 6-Item Screener, Visual Association Test, General Practitioner Assessment of Cognition, activities of daily living/instrumental activities of daily living, Benton's Orientation Test, Delayed Recall Test, and the Short Concord Informant Dementia Scale for dementia; AD8, St. Louis University Mental Status Exam, and Computer Assessment of Mild Cognitive Impairment for MCI) appear promising; however, their test performance has not been reproduced in other primary care–relevant populations. No studies directly addressed the adverse psychological effects of screening or adverse effects from false-positive or false-negative testing. One fair-quality study found that approximately half the older adults who screened positive for cognitive impairment refused to complete a formal diagnostic workup.

Treatment (Key Questions 4–5): We identified one systematic review and 131 additional studies that addressed the treatment or management of mild to moderate dementia and/or MCI.

Pharmacologic Interventions: Overall, based on one systematic review (50 trials) and 14 subsequently published trials evaluating donepezil, galantamine, rivastigmine, and memantine in people with mild to moderate dementia, these medications can improve global cognitive function in people with Alzheimer's Disease (AD) in the short-term. However, the magnitude of these changes is small, at approximately 1- to 3-point change on the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). The average effect of these changes is likely not clinically meaningful using commonly accepted values to interpret the clinical importance of these changes (4-point change on ADAS-cog over 6 months). Acetylcholinesterase inhibitors (AchEIs), but not memantine, appear to consistently improve measures of global functioning in people with AD in the short-term. Adverse effects from AChEIs are common. While there does not appear to be a difference in total serious adverse events for these medications across randomized trials, estimates of total serious adverse events appear higher in observational studies than in the trials. Trials evaluating other medications or dietary supplements (k=26; n=5,000), including low-dose aspirin, HMG-CoA reductase inhibitors (simvastatin and atorvastatin), nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, indomethacin, and celecoxib), gonadal steroids (estrogen plus or minus progesterone and testosterone), and dietary supplements (multivitamins, B vitamins, vitamin E plus or minus vitamin C, and omega-3 fatty acids) showed

no benefit on global cognitive or physical function in people with mild to moderate dementia or MCI.

Nonpharmacologic Interventions: We identified 59 fair- to good-quality trials evaluating the effect of multiple different types of interventions primarily aimed at the caregiver or the patient-caregiver dyad. Complex psychoeducational caregiver interventions (k=48; n=8,216) generally showed a small benefit (standardized effect size, approximately 0.2) on caregiver burden and depression outcomes. Although findings were somewhat inconsistent across cognitive intervention trials (k=15; n=1,128), cognitive stimulation plus or minus cognitive training appears to improve global cognitive function in the short-term for both people with MCI or dementia. Our ability to determine the magnitude and certainty of this benefit, however, is impeded by the limited number of trials and clinical (and statistical) heterogeneity, as well as the very wide confidence intervals (ranging from clinically not meaningful to a large effect). Harms were not reported in the included trials for caregiver or cognitive interventions. Exercise intervention trials (k=10; n=1,033) showed no consistent benefit on global cognitive outcomes or patient depression outcomes in people with MCI or mild to moderate dementia.

Limitations: Limitations include limited reproducibility of the test performance of instruments that are feasible to use in primary care; differences in estimates of test performance, which may be due to differences in populations or administration and scoring (choice of cut-point) of the instrument itself; and lack of clarity and standardization of defining MCI in diagnostic accuracy studies. Research in treatment of dementia other than AD is limited, and the average treatment effects of benefit for FDA-approved medications for AD and intensive interventions are small and generally in people with moderate dementia; thus, it is difficult to interpret its clinical importance and applicability for screen-detected patients. Other important measures of global functioning, such as health-related quality of life, global physical functioning, emergent or unexpected health care utilization, and institutionalization, are generally inconsistently reported.

Conclusions: We found no trial evidence that examined the effect of screening for cognitive impairment on patient, caregiver, or clinician decisionmaking or important patient, caregiver, or societal outcomes. Several brief screening instruments can adequately detect dementia, especially in populations with a higher prevalence of underlying dementia. Despite the size of this body of literature, only a handful of instruments have been studied as screening tests in more than one study. AChEIs, memantine, complex caregiver interventions, and cognitive stimulation all have evidence to support their use in mild to moderate dementia, specifically AD. However, the clinical importance of their benefit is unclear because the average effects of benefit observed in trials was small or had a large amount of imprecision.

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Chapter 1. Introduction

Scope and Purpose

The U.S. Preventive Services Task Force (USPSTF) will use this report to update its 2003 recommendation on dementia screening. In 2003, the USPSTF concluded that there was insufficient evidence to recommend for or against routine screening for dementia in older adults (I statement).[1] This recommendation was based on an evidence review that indicated that while some screening tests had good sensitivity, they had only fair specificity in detecting cognitive impairment and dementia.[2] While this review found evidence that several drug therapies had a beneficial effect on cognitive function, the magnitude of this benefit was small. Additionally, this review concluded there was insufficient evidence to determine whether the benefits observed in drug trials were applicable to screen-detected patients in primary care settings.

In 2011, we developed a work plan for this evidence review to address the previous review's evidence gaps and support the USPSTF in updating its previous recommendation. This updated recommendation is focused more broadly on screening for cognitive impairment, including both dementia and mild cognitive impairment (MCI). This evidence review was designed to assess 1) the net benefit and diagnostic accuracy of brief screening instruments to detect cognitive impairment in older adults, and 2) the net benefit of the commonly used treatment and management options for older adults with MCI or early dementia and their caregivers. Our review primarily focuses on screening adults in primary care, rather than specialty care settings (e.g., neurology or memory clinics), and the management of screen-detected people with cognitive impairment, excluding delirium. As a result, this review includes the treatment and management of people with MCI and mild to moderate dementia, as opposed to moderately-severe or severe dementia.

Background

Condition Definition and Etiology

Dementia is an acquired condition that is characterized by a decline in at least two cognitive domains (e.g., loss of memory, attention, language, or visuospatial or executive functioning) that is severe enough to affect social or occupational functioning.[3] Patients with dementia may also exhibit behavioral and psychological symptoms. The proposed Diagnostic and Statistical Manual, version 5 (DSM-V) subsumes dementia under a new syndrome, "major neurocognitive disorder."[4] Patients with major neurocognitive disorder experience a significant cognitive decline that is significant enough to interfere with independence in instrumental activities of daily living (IADLs), but this decline cannot be wholly due to delirium or another mental disorder, such as schizophrenia.

Based on its etiology, dementia can be classified as degenerative, vascular, or other. The major dementia syndromes in older adults include: Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), Parkinson's disease with dementia (PDD), and dementia of mixed etiology.[5] In AD, FTD, DLB, and PDD, abnormal

deposits that accumulate in the brain are believed to contribute to deterioration of brain function and dementia (amyloid plaques, neurofibrillary tangles, Lewy bodies).[6] Other neuropathological changes associated with dementia include: cortical atrophy, hemorrhages, small-vessel disease, and neural and white matter loss.[7] The exact etiological mechanisms for many types of dementia (e.g., AD, FTD, DLB, and PDD), however, have not been clearly defined.[8] For example, amyloid plaques and Lewy bodies found during brain autopsy are associated with AD and DLB or PDD, respectively. These pathological findings, however, are not always consistent with premorbid clinical diagnoses.[9] Other causes of cognitive impairment can include depression, alcohol abuse, medications (e.g., antihistamines, anticholinergics), metabolic disorders (e.g., thyroid disorders), intracranial tumors, normal pressure hydrocephalus, subdural hematomas, infections (e.g., HIV, prion diseases), traumatic brain or anoxic injury, and rare neurodegenerative disorders (e.g., Huntington's disease, progressive supranuclear palsy).[10,11]

MCI is distinguished from dementia in that cognitive impairment is not severe enough to interfere with independence in daily life (e.g., IADLs). Researchers describe this condition using various terminology that includes differences in diagnostic criteria and underlying constructs, such as MCI, cognitive impairment no dementia (CIND), age-related cognitive decline (ARCD), mild neurocognitive disorder, and mild cognitive disorder.[12] The International Working Group on Mild Cognitive Impairment established the current, and perhaps most commonly used, criteria for MCI as: cognitive decline as evidenced by self and/or informant and/or clinician report and impairment on objective cognitive tasks, and/or evidence of decline over time on objective tasks; preserved basic activities of daily living (ADLs) (or minimal impairment in complex instrumental functions); and does not meet DSM-IV, ICD-10 criteria for a dementia syndrome.[13] This definition contrasts with earlier working definitions, most commonly the definition Petersen and colleagues developed in 1999 (which focused on amnestic MCI): memory complaint (corroborated by an informant), memory impairment on objective testing, normal performance in nonmemory cognitive domains, preserved ADLs, and no dementia.[14,15] While the exact definition of MCI is evolving, experts in this field have proposed several subtypes, including amnestic and nonamnestic MCI, as well as single- or multidomain MCI.[16-18] MCI is thought to be an intermediate phase between normal cognition and dementia.[18] The proposed changes to DSM-V introduce "mild neurocognitive disorder," which subsumes MCI and other related entities such as CIND and ARCD. Mild neurocognitive disorder is characterized by cognitive impairment that, while not severe enough to interfere with IADLs, may require compensatory strategies.[4]

Prevalence and Burden of Disease

Dementia

While the exact prevalence of dementia is unknown, we know that dementia is a common and costly condition. Researchers estimate that dementia affects between 2.4 to 5.5 million Americans.[5,7,19] By 2050, the prevalence of AD is projected to be 13.8 million people in the United States, with approximately 1 million new cases a year.[20] The estimated total health, long-term, and hospice care costs for dementia in the United States were $200 billion in 2012. Medicare and Medicaid pays approximately 70 percent of these costs, representing $140 billion. These costs do not include the estimated $210 billion in uncompensated care that informal

caregivers provide anually.[20]

The prevalence of dementia is strongly related to increasing age. Attempts to provide prevalence estimates have arrived at slightly different estimates. Data from large population-based surveys indicate that the prevalence of dementia in the United States is 5 percent in individuals ages 71 to 79 years, rising to 24 percent at ages 80 to 89 years, and 37 percent in those older than age 90 years.[5] These prevalence estimates, however, are highly dependent on the methods and operational criteria used for diagnosis.[21] An international Delphi consensus and review of published dementia prevalence studies estimated mean prevalence in the United States and Canada at 0.8 percent (standard deviation [SD], 0.1) in individuals ages 60 to 64 years, 1.7 percent (SD, 0.1) in individuals ages 65 to 69 years, 3.3 percent (SD, 0.3) in individuals ages 70 to 74 years, 6.5 percent (SD, 0.5) in individuals ages 75 to 79 years, 12.8 percent (SD, 0.5) in individuals ages 80 to 84 years, and 30.1 percent (SD, 1.1) in individuals age 85 years or older.[22]

The prevalence of dementia also varies by race and ethnicity. A recent population-based study found the prevalence of dementia in adults age 71 years and older was 21.3 percent for blacks compared with 11.2 percent for whites.[23] Dementia also affects more women than men. In individuals age 71 years and older, approximately 16 percent of women have dementia compared with 11 percent of men.[20] Although research has revealed significant differences in the prevalence of dementia based on sex,[5] this difference is not seen in incidence rates. These differences are primarily explained by women's longer life expectancy rather than any sex-based risk factors.[20]AD accounts for between 60 to 80 percent of all dementia, while FTD accounts for 12 to 25 percent, 10 to 20 percent are considered VaD, 5 to 10 percent are DLB, and between 10 to 30 percent are dementia with mixed etiologies.[5,19,24] The proportions of dementia caused by each of these etiologies, however, varies widely between studies due to differences in diagnostic criteria, study setting, and age of participants. One systematic review of the etiology of dementia identified 39 studies, a third of which included community-based populations.[25] This review found AD accounted for 56.3 percent of cases, followed by VaD (20.3%) and mixed etiologies (6.2%). Other causes were much less common and included PDD (1.6%), metabolic (1.1%), intracranial tumors (1.1%), normal pressure hydrocephalus (1.0%), depression (0.9%), alcohol abuse (0.6%), subdural hematoma (0.3%), infections (0.3%), trauma (0.2%), anoxic brain injury (0.2%), medications (0.1%), and Huntington's disease (0.1%).[25] About 4 percent of dementia cases in nine of the 12 community-based studies included in that review were due to potentially reversible causes. Actual reversal of symptoms, however, occurred in much smaller proportions. Indeed, only 0.6 percent of dementia cases actually reversed to normal cognition in studies that reported followup.[25] Reversible causes of dementia may occur more frequently in younger patients, those with more recent onset of symptoms, and those with mild symptoms.

While AD is the single most common type of dementia overall, its prevalence varies across ethnic groups. Studies have found that the prevalence of AD in elderly blacks is roughly double (10.5% vs. 5.4%) the prevalence in nonHispanic whites.[26] The prevalence of AD in Hispanics is approximately 1.5 times that observed in the white population.[23,27,28] Epidemiological data suggests that certain risk factors are more common in blacks and Hispanics than whites, such as hypertension, coronary artery disease, and stroke, which may account for some of the racial disparities observed in AD.[27] There is little consensus, however, on the cause for observed disparities in prevalence.

MCI

The prevalence of MCI is even more difficult to ascertain due to between-study differences in sampling and methods of clinical assessment. Available studies also have important differences in the criteria used to define the condition.[29] Varying definitions and terminology (e.g., MCI, CIND, ARCD) hinders our ability to estimate the true prevalence of cognitive impairment without functional limitations. These estimates range widely from 3 to 42 percent in adults age 65 years and older and vary depending on the population and diagnostic criteria used.[29,30] One systematic review that included 35 population-based studies found the median prevalence was 4.9 percent (range, 0.5% to 31.9%) for amnestic MCI, 26.4 percent (range, 3% to 42%) for MCI, 20.6 percent (range, 5.1% to 35.9%) for CIND, and 15.6 percent (range, 3.6% to 38.4%) for age-associated memory impairment, across a broad age range of older adults.[30] While the prevalence of MCI and CIND appear to increase with age,[30] these studies did not identify a consistent relationship with age across different definitions.[29,30] Likewise, these studies found no consistent relationship between MCI and sex, race/ethnicity, or education.[29,30]

Natural History

Dementia

The most common types of dementia are irreversible and usually progressive, including AD, FTD, VaD, and DLB. Early stages of dementia generally affect IADLs along with the ability to learn and retain new information. As dementia progresses, patients are unable to carry out basic ADLs.[31,32] The onset and progression of dementia is highly variable and depends on the etiology or type. The median survival time from diagnosis of dementia is estimated to range from 4.5 to 6.7 years, although this varies by how onset of disease is defined, the degree of impairment at diagnosis, age at diagnosis, and the type of dementia.[33,34] For example, median survival time for AD is thought to be longer than for FTD; some patients can live as long as 20 years with AD.[20,35-37] The rate of progression of cognitive decline also varies with the type of dementia. Patients with AD, for example, can experience a decline of 2 points or less per year on the Mini Mental State Examination (MMSE), whereas the decline in those with other types of dementia can be somewhat more rapid (e.g., decline of 2 to 4 MMSE points annually).[38] The rate of decline, however, can also depend on the stage of disease, and patients may experience an accelerated rate of decline as their disease progresses.[39,40] In addition to cognitive decline, neuropsychiatric symptoms can also accompany dementia, such as psychotic symptoms (e.g., delusions, paranoia, and hallucinations), depressive symptoms, apathy, and agitation or aggression, as well as personality changes.[6] Neuropsychiatric symptoms can occur with any type of dementia, although different neuropsychiatric symptoms are more common with specific types. FTD, for example, is commonly associated with euphoria or disinhibition, whereas PDD and DLB are commonly associated with hallucinations.[41-44]

MCI

MCI may have some clinical utility for predicting later dementia. While the level of cognition remains stable over time in the majority of individuals with MCI, smaller proportions will experience either a return to normal cognition or worsening cognition, resulting in functional

impairment and progression to dementia. The rates of stability, progression, and regression of MCI vary markedly between studies. Again, this variation likely reflects the complex underlying pathology, differences in diagnostic criteria, and differences in population settings and participants. Variations in diagnostic criteria have real implications for understanding the natural history of MCI. For example, the 1999 Petersen criteria define MCI as amnestic MCI versus broader criteria which include amnestic and nonamnestic, along with single- and multidomain dementia. This distinction is important because amnestic MCI is more likely to represent underlying AD or a similar condition and therefore progress to dementia. Likewise, multidomain MCI is more likely to progress to dementia.[45] Single-domain MCI is often a precursor of multidomain MCI; therefore, single-domain impairment may be the earliest detectable stage of a progressive condition, but also more likely to revert to normal.[45-47] Differences in populations also have implications on understanding the natural history of MCI. There is a selection bias of people with MCI in clinical studies as opposed to community-based studies. People seeking care for mild cognitive deficits, for example, may be more likely to have an underlying dementia disease, fewer comorbid conditions, more behavioral symptoms, or be at a later/more severe stage of disease.[48]

A recent systematic review of 41 cohort studies examining the progression from MCI to dementia provides strong evidence that individuals with MCI have a much greater risk of progressing to dementia compared with individuals with normal cognition.[17] In a subset of five studies, the annual conversion rate to dementia over a mean followup of 6.0 years was 3.6 percent for individuals with MCI compared with 0.43 percent for healthy subjects (relative risk [RR], 13.8 [95% CI, 8.44 to 22.6]). Overall, the annual rate of progression from MCI to dementia in community settings (adjusted for sample size and dementia type) was 4.9 percent (95% CI, 1.6 to 9.9). The adjusted rate from MCI to AD was 6.8 percent (95% CI, 1.9 to 14.5) and 1.6 percent (95% CI, 0.3 to 9.4) from MCI to VaD.[17] Studies using different definitions of MCI found similar rates of progression. The cumulative rate of progression for MCI to dementia was 22 to 40 percent in these studies, which had mean study periods of 5 to 10 years. Despite these rates of progression, MCI may also regress to normal cognition over time in 10 to 40 percent of individuals with MCI.[45,49,50] Additionally, patients who revert to normal cognition may also later progress to dementia, which complicates these progression estimates.[51] Although several population-based studies have noted an increased risk of mortality in people with MCI compared with those with normal cognition,[52-56] the literature is not consistent because other studies have found no associated increase in mortality.[57,58]

Risk Factors for Cognitive Decline and Factors Associated With the Reduction of Risk of Cognitive Decline in Older Adults

Increasing age is the strongest known risk factor for cognitive decline in general and for AD specifically.[19] Other risk factors for cognitive decline and dementia have been proposed, however, and each carries with it a varying evidence for strength of association. The ε4 allele of the lipoprotein E gene has good observational evidence in whites (and Asians) as a risk factor for AD.[59] Other risk factors for cognitive decline or dementia with lower-quality observational evidence include cardiovascular risk factors (e.g., diabetes, tobacco use, hypercholesterolemia, hypertension, metabolic syndrome, obesity), depression, physical frailty, low educational level, low social support, and having never been married.[59-62]

In contrast, several dietary and lifestyle factors have been associated with a decreased risk of dementia, including adequate folic acid intake, low saturated fat and longer-chain omega-3 fatty acids intake, high fruit and vegetable intake, Mediterranean diet, moderate alcohol intake, educational attainment, cognitive engagement, and participation in physical activity.[59,62-65] It is important to note, however, that the evidence supporting these associations is weaker than the evidence for the factors that are associated with increased risk of dementia.

Rationale for Screening in Older Adults

Primary care clinicians may fail to recognize cognitive impairment during clinic visits using routine history and physical examination.[19,66] As many as 29 to 76 percent of patients with dementia or probable dementia are not diagnosed by primary care physicians.[67-69] Moreover, the sensitivity of a clinician's diagnosis appears to be strongly related to dementia severity.[70] Because of this, most people with dementia are not diagnosed until they are at moderate to severe stages of the disease. Therefore, screening tests in all or targeted older adults may help identify patients with dementia or MCI who are otherwise missed. Early identification of cognitive impairment would ideally allow patients and their families to receive care at an earlier stage in the disease process, leading to improved prognosis and decreased morbidity.

Early identification of cognitive impairment potentially facilitates discussions regarding decisionmaking (e.g., health care, financial, or legal) while the patient still retains decisionmaking capacity. Clinical experts and researchers have suggested that the health, psychological, and social benefits from early recognition of dementia include: early education of caregivers on how to manage the patient; advanced planning (e.g., establishing a will, health care proxy, power of attorney, advanced directives, timely discussion of care transitions and appropriate placement options); reduced patient and family anxiety and stress, as well as reduced caregiver burden, blame, and denial; patient safety (e.g., monitoring driving, medication compliance, cooking); and promotion of advocacy for research and treatment development.[71]

Knowledge of the patient's cognitive status is important for the management of comorbid conditions. Nearly all older adults with cognitive impairment have one or more serious comorbid conditions and take multiple medications.[72] Cognitive impairment can affect the management of these comorbid conditions and may lead to worsened outcomes of the comorbid conditions. Cognitive impairment may lead patients to report symptoms and health behaviors inaccurately, may decrease their ability to consent to treatments, may make medication adherence challenging, and may make followup of chronic conditions sporadic or nonexistent. Medication management of comorbid conditions may pose higher risks in people with cognitive impairment. Treating incontinence with anticholinergic medications, for example, can worsen cognition, as can treatment of chronic pain with opioids or tricyclic antidepressants.[73] In addition, cognitive impairment may limit quality of life and life expectancy in patients with other chronic conditions, which makes patients less likely to realize a benefit and more likely to realize harm from aggressive or invasive treatments.[74,75] These benefits of early diagnosis may make screening valuable even if it is unclear whether early treatment alters the natural history of dementia by preventing or slowing the rate of cognitive decline.[59]

Clinicians can employ many different brief cognitive screening instruments in primary care.

Instruments that take 10 minutes or less to administer, for example, may include: the MMSE, Clock Draw Test (CDT), Mini-Cog, St. Louis University Mental Status Exam (SLUMS), Abbreviated Mental Test (AMT), Blessed Orientation Memory Test, General Practitioner Assessment of Cognition (GPCOG), Short Portable Mental Status Questionnaire (SPMSQ), and Montreal Cognitive Assessment (MoCA).[19,76-80] In addition to brief tests, more extensive screening and diagnostic instruments are available for use in secondary care or other settings, although their longer administration time (10 to 45 minutes) render them infeasible for use in primary care.[81]

Diagnostic Workup of Cognitive Impairment

These brief cognitive tests are generally not diagnostic of dementia or MCI. A positive screening test triggers subsequent diagnostic testing that assesses the level and possible etiology of cognitive impairment. In addition to a more detailed and focused clinical history and physical examination, this diagnostic workup may also include more comprehensive cognitive and functional assessments (e.g., neuropsychological testing or clinical evaluation by a trained clinician), laboratory tests to identify potentially reversible causes of dementia due to treatable underlying disorders (e.g., hypothyroidism, vitamin B12 deficiency), and sometimes structural and functional imaging of the brain (e.g., computed tomography [CT], magnetic resonance imaging [MRI], single-photon emission CT, and positron emission tomography [PET]).[82] Neuropsychological testing involves a detailed evaluation of each of the multiple cognitive domains. A diagnosis of dementia requires that the patient has developed requisite cognitive deficits (impairments in learning and memory, language, or visuospatial or executive function), which can be established with specific tests and interpreted relative to appropriate norms. The American Academy of Neurology (AAN) recommends screening for B12 deficiency and hypothyroidism and neuroimaging with noncontrast head CT or MRI in all patients with dementia.[83] Currently, however, there is no evidence to support or refute routine laboratory testing or neuroimaging as part of the routine diagnostic workup of cognitive impairment. As a result, each individual's clinical presentation should guide further testing. Genetic testing for autosomal dominant genes for AD (APP, PS1, PS2) are appropriate only in early-onset familial cases. Genetic testing for APOEε4 allele has been studied as a susceptibility marker and is not useful in the diagnostic workup of cognitive impairment.

Additional diagnostic tools are currently in development.[84,85] Cerebrospinal fluid (CSF) and plasma and urine biomarkers (e.g., amyloid beta peptides, tau, and molecular markers) to diagnose AD and other types of dementia are still at the discovery stage or undergoing initial validation for use in early dementia or MCI.[86] Recent research shows promise for using plasma biomarkers to screen for different types of dementia, with model predictions showing sensitivity and specificity of up to 80 and 90 percent, respectively.[87,88] Imaging techniques, such as MRI, diffusion tensor imaging, CT, magnetic resonance spectroscopy, and PET scans are also being evaluated to aid in the diagnostic workup of dementia or MCI.[89-92] None of these biomarker or imaging tools have been evaluated for screening purposes.

Interventions and Treatments for Cognitive Impairment

Treatment for cognitive impairment seeks to improve quality of life and maximize functional

performance by addressing cognitive, mood, and behavioral impairments,[82] as well as to treat any modifiable or reversible causes of impairment.

Interventions Aimed at Cognitive Decline

There are multiple pharmacologic and nonpharmacologic interventions aimed at (permanently or temporarily) preventing, slowing, or reversing cognitive decline in older adults. In support of a 2010 National Institutes of Health State of the Science Conference Statement on Preventing Alzheimer Disease and Cognitive Decline,[93] Plassman and colleagues conducted a systematic review of factors associated with reduction of risk of cognitive decline and the net benefit of interventions to improve or maintain cognitive ability or function.[59] The review found moderate- to high-quality evidence that treatment with vitamins (i.e., multivitamins, vitamins B6 and B12, folic acid, vitamins C and E, and beta-carotene), postmenopausal hormone replacement therapy, HMG-CoA reductase inhibitors, aspirin, dehydroepiandrosterone (DHEA), or acetylcholinesterase inhibitors (AChEIs) does not prevent cognitive decline in mild to moderate dementia.[59] Another targeted review of U.S. Food and Drug Administration (FDA)-approved pharmacologic interventions for AD, in support of a joint American College of Physicians (ACP) and American Academy of Family Physicians (AAFP) clinical practice guideline, concluded that many of the statistically significant improvements in scores on various instruments to evaluate changes in patients with dementia were very small or had short durations of effect, so that these changes were not clinically important (or the clinical importance could not be determined).[94]

There is some evidence, however, that suggests that nonpharmacologic treatments decrease rates of cognitive decline. The systematic review by Plassman and colleagues identified high-quality evidence to support cognitive training, as well as observational evidence to suggest that lifestyle behaviors (e.g., Mediterranean diet, vegetable intake, omega-3 fatty acids, physical activity, and nonphysical leisure activity) were associated with a decreased rate of cognitive decline.[59]

Interventions to Improve Patient or Caregiver Quality of Life

Informal family caregivers provide about 80 percent of home care for people with dementia.[95] Care for people with dementia can be difficult, and informal caregivers often have high levels of depression and stress. As a result, caregiving may lead to a negative impact on the caregiver's health and employment and the family's finances.[20,96] Available evidence suggests that interventions to improve caregiver or dyad (patient and caregiver) quality of life may improve patient and caregiver outcomes. Two independently conducted systematic reviews, which included studies of psychosocial interventions aimed at caregivers of community-dwelling people with dementia, showed that some interventions can indeed reduce caregiver morbidity and delay institutionalization of people with dementia.[97,98]

Experimental Therapies

Available research has evaluated very few interventions specifically in people with MCI or mild (or earlier stage) dementia. Disease-modifying therapies to slow cognitive decline is an extremely active area of research, and promising therapies include: intravenous immunoglobulin (IVIG), growth hormone-releasing hormone (GHRH), and various immunotherapies targeting

beta-amyloid.[99-101]

Current Clinical Practice and Recommendations of Other Groups

Currently, diagnosis of dementia is initiated mostly based on a clinician's suspicion of patient symptoms or caregiver concerns.[102] As many as 29 to 76 percent of patients with dementia or probable dementia, however, are not diagnosed by primary care physicians.[67-69] Although no professional organizations explicitly recommend screening for dementia in asymptomatic adults, many groups (including the USPSTF, AAN, American Geriatrics Society, and European Federation of Neurological Societies) have recommended assessing the cognitive abilities of older adults who present with cognitive or cognitive-related functional complaints.[1,82,83,103] The onset of dementia can be insidious and the early symptoms of dementia are extremely common, which could also contribute to the possible underdiagnosis of dementia. For example, about 40 to 50 percent of older adults report subjective memory complaints.[70] Cognitive or cognitive-related functional complaints, however, may not be apparent during routine office visits unless they are directly assessed, and individuals with subjective memory complaints often have normal cognition when tested. Additionally, barriers that may contribute to missed or delayed diagnosis of dementia include: physician and patient lack of knowledge, physicians' concerns about overdiagnosis and labeling, lack of appropriate assessment tools, difficulty in communication of diagnosis, and the patient's refusal to be assessed for dementia, as well as time and financial constraints.[70]

In 2011, Medicare began covering the "detection of cognitive impairment" as a part of the new Annual Wellness Visit benefit, which was mandated by the Affordable Care Act.[104] Currently, however, the recommendations issued by the Centers for Medicare and Medicaid Services (CMS) provide little guidance on recommended screening instruments or techniques, other than directing providers to use direct observation and consider information from informants.[105] In 2013, the Alzheimer's Association published recommendations for operationalizing the detection of cognitive impairment during the Annual Wellness Visit, and recommended the use of a brief structured assessment (i.e., GPCOG, Mini-Cog, Memory Impairment Screen [MIS], AD8, or short Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE]) if signs or symptoms of cognitive impairment are present upon review of a health risk assessment, through clinical observation or self-reported (patient or informant) concerns.[106]

Chapter 2. Methods

The USPSTF will use this evidence review to update its 2003 USPSTF recommendation statement on screening for cognitive impairment in primary care. To accomplish this, our review assesses 1) the net benefit and diagnostic accuracy of brief screening instruments to detect cognitive impairment in older adults, and 2) the net benefit of the major treatment and management options for older adults with MCI or early dementia and their caregivers.

This review's scope differs from that of the 2003 evidence review in two important ways.[2] First, we broadened the scope to include MCI screening and treatment, in addition to dementia screening and treatment. In practice, clinicians use screening tests to detect cognitive impairment, which includes both dementia and MCI. MCI is increasingly viewed as a preclinical stage to dementia and clinicians may also be treating or intervening earlier in the disease process (e.g., off-label use of pharmacologic agents).[107] Second, we broadened the framework to address the impact of screening and/or diagnosis of cognitive impairment on decisionmaking by the patient, family/caregiver, or clinician. Our decision to add decisionmaking outcomes reflects the importance of developing an accurate understanding of cognitive ability for patient, family, and clinician planning, as well as care delivery.

Analytic Framework and Key Questions

The analytic framework is presented in **Figure 1**.

Screening Key Questions (1–3)

Key Question 1. Does screening for cognitive impairment (dementia or MCI) in community-dwelling older adults in primary care–relevant settings improve decisionmaking, patient, family/caregiver, or societal outcomes?

Key Question 2. What is the test performance of screening instruments to detect MCI and/or dementia in community-dwelling older adult primary care patients?

Key Question 3. What are the harms of screening for cognitive impairment?

Treatment/Management Key Questions (4, 5)

Key Question 4. Do pharmacological or nonpharmacologic interventions for MCI and/or early dementia in older adults improve decisionmaking, patient, family/caregiver, or societal outcomes?

Key Question 5. What are the harms of pharmacological or nonpharmacologic interventions for cognitive impairment?

Definitions of Terms Used in Key Questions

- **Cognitive impairment:** Dementia or MCI. Cognitive impairment in this report does not include delirium.
- **MCI:** Loosely defined term that encompasses cognitive impairment that does not interfere with independence in daily life. Mutually exclusive from dementia.
- **Early dementia:** Mild or moderate dementia. Traditionally, an MMSE score of 21 to 24 is considered mild dementia and a score of 13 to 20 is considered moderate dementia.
- **Screening:** Methodically administering an instrument to patients in order to detect a disease/condition in "apparently" healthy individuals. The term screening, in this report, is in contrast to "case-finding," which is testing targeted to individuals or groups who are suspected to be at risk for a particular disease/condition. Case-finding (as opposed to diagnostic testing) involves actively and systematically searching for at-risk people, rather than waiting for them to present with obvious symptoms or signs of active disease.
- **Screening instruments:** Instruments designed to assess cognitive function that take 10 minutes or less to administer by clinic staff or 20 minutes or less to self-administer (by patient or informant).
- **Community-dwelling older adults:** Adults who live at home or in senior living communities, assisted living, adult foster care, or residential care facilities. This excludes institutionalized people who reside in intermediate care facilities (i.e., rehabilitation centers or skilled nursing facilities).
- **Primary care–relevant settings:** Primary care, outpatient settings (ambulatory care). This excludes hospitals, emergency departments (EDs), or specialty (referral) outpatient settings (i.e., memory, dementia, geropsychology, or neurology clinics).
- **Decisionmaking outcomes:** For patients and family/caregivers: health care, legal, and financial planning (e.g., advanced directives); safety planning; and living arrangements. For clinicians: health care planning, including advanced directives; patient and caregiver education; safety planning (change, monitored medication use); screening and diagnostic decisions (e.g., cancer screening); and other treatment or management decisions (e.g., treatment of reversible causes of dementia, management of comorbid conditions). Test performance: sensitivity, specificity, predictive values, likelihood ratios, or area under the curve.

Data Sources and Searches

Given the breadth and volume of literature for this topic, we first conducted a search for recent existing systematic reviews addressing both the screening and treatment key questions, using MEDLINE, Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and publications from the Institute of Medicine, the Agency for Healthcare Research and Quality (AHRQ), and the National Institute for Health and Clinical Excellence (NICE) (**Appendix A**). This search identified 771 potentially relevant reviews on screening or treatment for dementia and 283 additional potentially relevant reviews on screening or treatment for MCI. We used the most relevant existing systematic reviews, one screening for dementia review,[19] and 11 treatment of dementia and MCI reviews[108-118] to develop a comprehensive search strategy from the end of the existing systematic review (if available) until December 10, 2012. Existing

systematic reviews were primarily used to locate studies for inclusion (as part of our search strategy). However, in one instance, we used a recent, good-quality systematic review commissioned by AHRQ to summarize the primary results for FDA-approved medications to treat AD (i.e., donepezil, rivastigmine, galantamine, tacrine, and memantine), on a variety of outcomes.[119] This review by Santiguida and Raina was subsequently published in *Annals of Internal Medicine* with an updated search through 2006 by Raina and colleagues.[110] We supplemented this body of literature with newly identified trials and their open-label extension (OLE) studies through our own literature searches that incorporated the searches used in the existing (original) systematic review.

In many cases, existing systematic reviews were not available for the screening or treatment of MCI. In these instances, we searched from 1990 to December 10, 2012 because MCI was not widely recognized as a clinical entity until 1991.[120] We searched MEDLINE, PsycINFO, and the Cochrane Central Register of Controlled Trials to locate relevant studies for all key questions. We supplemented our searches with expert suggestions and through reviewing reference lists from all other recent relevant existing systematic reviews. We also searched selected grey literature sources, including ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, and Current Controlled Trials (ISRCTN Register) for ongoing trials.

Study Selection

Two investigators independently reviewed 16,179 abstracts and 1,190 articles (**Appendix A Figure 1**) against the specified inclusion criteria (**Appendix A Table 2**). We resolved discrepancies through consensus and consultation with a third investigator. We excluded articles that did not meet inclusion criteria or were rated as poor quality. These trials are listed in **Appendix B**.

For screening questions (Key Questions 1–3), we included studies that evaluated any brief screening instrument that could be delivered in primary care in 10 minutes or less by a clinician or self-administered in 20 minutes or less. We excluded instruments with longer administration times (e.g., modified MMSE, Addenbrooke's Cognitive Examination), as these cannot be reasonably administered in primary care, although many are used in specialty care settings, such as neurology or memory clinics. Screening instruments could be administered to the patient or their family member or caregiver (informant) in person or by telephone. We excluded all diagnostic imaging (e.g., CT, MRI, PET), or biomarker testing (e.g., CSF, plasma, or urine), as these may be used as part of a diagnostic workup for cognitive impairment, rather than as screening tests (and/or are still considered investigational/experimental tests). Diagnostic accuracy studies of screening tests had to compare the index test with a reference standard (i.e., clinical assessment or neuropsychological testing, with explicit diagnostic criteria with or without expert consensus/conference). We excluded diagnostic accuracy studies that only compared the index test with another screening test (e.g., MMSE). We included studies that were relevant to community-dwelling older adults being seen in primary care in the United States. As a result, we excluded screening studies in hospitals or intermediate care facilities (i.e., nursing homes, rehabilitation facilities, and subacute care facilities) or studies conducted in developing countries (those rated as high, medium, or low on the 2011 Human Development Index[121]). However, we included studies in noninstitutionalized older adults living in senior communities,

assisted living facilities, adult foster care homes, or residential care. We also excluded screening studies in which populations were selected from referred settings (e.g., memory, neurology, psychogeriatric, or geriatric clinics in nonU.S. settings that serve a consultant role, Alzheimer's Disease Research Centers).

Screening studies had to include decisionmaking outcomes, patient health or safety outcomes, family or caregiver burden or health outcomes, or societal outcomes (Key Question 1) or include diagnostic accuracy (sensitivity, specificity for dementia or MCI) outcomes (Key Question 2) or harms (unwanted or unexpected direction of effect on health outcomes, psychological harms, harms due to labeling, poor adherence to diagnostic followup) (Key Question 3). Screening studies for Key Question 1 were limited to good-quality systematic reviews; randomized, controlled trials (RCTs); or controlled clinical trials (CCTs). Studies included for Key Question 2 were limited to good-quality systematic reviews or prospectively conducted diagnostic accuracy studies. We excluded case-control studies in which cases were selected based on having known dementia or MCI. Distorted selection of patients in selective recruitment or case-control designs have repeatedly been shown to overestimate sensitivity.[122-126] Although a distorted selection of patients directly affects the applicability of the study findings (and predictive values due to prevalence of underlying disease), we excluded case-control studies from our review because of the threats to validity (i.e., spectrum bias). Spectrum bias refers to the phenomenon that the diagnostic test performance may change between clinical settings due to changes in patient case-mix. We considered any study design for Key Question 3 except for case series and case reports.

We did not have the resources to review all possible treatment modalities for treatment or management questions (Key Questions 4 and 5). As a result, we focused on the major pharmacologic and nonpharmacologic interventions intended for use during the earlier stages of dementia. For this review, we included FDA-approved medications used to treat patients with AD for the purpose of preventing/delaying cognitive decline (i.e., donepezil, galantamine, rivastigmine, tacrine, memantine); medications primarily aimed at cardiovascular risk reduction for treatment of VaD, including antiplatelet medications, antihypertension medications, and HMG-CoA reductase inhibitors; nonsteroidal anti-inflammatory drugs (NSAIDs); gonadal steroids (i.e., estrogen, progesterone, testosterone); and dietary supplements (i.e., vitamins, minerals, antioxidants). We excluded nonFDA-approved AChEIs (e.g., metrifonate, velnacrine); medications aimed at neuropsychiatric symptoms (i.e., antidepressants, antiepileptics, antipsychotics); medications without FDA approval for the treatment of cognitive impairment (e.g., glitozones, nicergoline, piracetam, posatirelin, selegiline, sabeluzole); all experimental drug therapies (e.g., antiamyloid disease-modifying treatments, IVIG, GHRH); medical foods and nutritional interventions; and herbal supplements (e.g., gingko biloba, DHEA, L-carnitine, hyperzine, curcumin) (**Appendix C Table 1**). We also included a broad range of nonpharmacologic interventions aimed at patients or their nonprofessional caregivers. We defined caregivers as those who are, or are about to be, engaged in taking some kind of responsibility for the care of the patient. They have some existing relationship to the patient, such as spouse/partner, relative, or friend. Specifically, nonprofessional caregivers have no formal training as caregivers and are nonsalaried, although they may (often) receive some financial compensation for their role. Nonpharmacologic interventions include multidisciplinary or multicomponent interventions aimed at the patient or dyad, peer support interventions aimed at the caregiver, education-only interventions aimed at the patient or dyad, cognitive training

(with or without motor training) or cognitive rehabilitation interventions aimed at the patient, cognitive stimulation interventions aimed at the patient, and exercise interventions aimed at the patient or caregiver.

We only included treatment studies that were conducted in community-dwelling older adults with MCI or mild to moderate dementia. Due to our focus on the treatment and management of screen-detected people with cognitive impairment, we excluded treatment studies that focused on moderately-severe or severe dementia or patients exclusively in hospitals or intermediate care facilities. Therefore, we also excluded interventions primarily aimed at noncognitive symptom management (e.g., music, light, pet, reminiscence, or psychodynamic interpersonal therapy; nighttime home monitoring systems; snoezelen) and respite care or day care interventions designed for patients with more significant symptoms and/or functional limitations, which are therefore less representative of screen-detected people. We also excluded primary prevention trials in which treatment was aimed at preventing or delaying the onset of cognitive impairment in healthy older adults without known cognitive impairment. We included treatment or management studies with outcomes on decisionmaking for patients and family or clinicians (e.g., health care planning, including advance directives; screening and diagnostic decisions; safety planning; legal and financial planning); patient health outcomes (e.g., cognitive function, physical function, overall function, health related quality of life [HRQL], safety, medication use/adherence, neuropsychiatric symptoms [insomnia, depression, agitation, aggression, wandering], ED use, hospitalizations, or institutionalization); caregiver outcomes (e.g., caregiver burden, HRQL); or societal outcomes (e.g., automobile accidents). We excluded studies if they only included patient satisfaction or cost outcomes. Treatment effectiveness studies (Key Question 4) were limited to good-quality systematic reviews of trials or RCTs/CCTs with a control group. As such, we excluded comparative effectiveness trials without a usual care, placebo, wait-list, or minimally active control group. For example, we excluded trials that explicitly compared two active interventions (e.g., cognitive stimulation vs. cognitive training, skills-based vs. support-based education, general occupational vs. tailored occupational therapy).

For harms (Key Question 5), we only searched for harms on interventions that were shown to have a potential benefit (i.e., any evidence of efficacy). We primarily focused on serious harms that resulted in unexpected medical care, morbidity, or mortality. We report on less serious harms, namely adverse effects (and discontinuation rates as a proxy for adverse effects) of medications, from trials or observational studies with comparator populations. We included all trials that were included for the efficacy questions (Key Question 4), OLEs of included drug trials, and larger trials or observational studies (cohort or case-control studies with $n \geq 1{,}000$). We excluded smaller trials (not meeting criteria for Key Question 4) and cohort studies ($n < 1{,}000$) because these studies did not have power to detect rare events, were nearly all shorter-term (<1 or 2 years followup), and/or were conducted in selected populations. As a result, these studies did not add any new information on harms to the included trial literature (Key Question 4) or included larger observational studies. We excluded case series and case reports.

We only included studies that published their results in the English language.

Data Extraction and Quality Assessment

For screening studies, we extracted details about each study's screening instrument(s) (e.g., administration time, language, cut-point); recruitment and inclusion criteria; sample sizes (n) recruited, eligible, and analyzed; patient characteristics (e.g., age, sex, race/ethnicity, education); prevalence (proportion) of dementia and/or MCI; reference standard (e.g., how it was conducted, diagnostic criteria, whether applied to all or a subset); diagnostic outcomes for given cut-points (e.g., raw numbers, sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, area under the curve); and any reported adverse effects. For treatment trials, we extracted details about each study's intervention(s) (e.g., description, intervention components, dose/intensity, frequency and duration) and control group(s); recruitment and inclusion criteria; sample sizes (n) recruited, eligible, and analyzed; patient characteristics (e.g., age, sex, race/ethnicity, education); prevalence (proportion) of dementia and/or MCI; any decisionmaking outcomes; any societal outcomes; and important patient outcomes (i.e., mortality, institutionalization, hospitalizations, ED visits, measures of cognitive function [global and domain-specific measures], measures of global physical function, measures of overall function and HRQL, measures of neuropsychiatric symptoms [global and symptom-specific measures], measures of caregiver burden, and any adverse events). We present diagnostic studies that evaluated more than one screening instrument and trials with multiple intervention arms in multiple tables, if appropriate. A second reviewer verified all extracted data.

At least two reviewers critically appraised all articles that met inclusion criteria using the USPSTF's design-specific quality criteria (**Appendix A Table 3**).[127] We supplemented this criteria with NICE methodology checklists,[128] Assessment of Multiple Systematic Reviews for systematic reviews,[129] Newcastle Ottawa Scales for cohort and case-control studies,[130] and Quality Assessment of Diagnostic Accuracy Studies for studies of diagnostic accuracy.[131] We rated articles as good, fair, or poor quality. In general, a good-quality study met all criteria well. A fair-quality study did not meet, or it was unclear if it met, at least one criterion, but also had no known important limitations that could invalidate its results. A poor-quality study had a single fatal flaw or multiple important limitations. The most common fatal flaw for diagnostic studies included application of the reference standard to only those patients who screened positive (because when missing data is not random or selective, analysis will generate biased estimates of diagnostic accuracy,[123-125,132] and verification of only screen-positive patients will generally lead to an overestimation of both sensitivity and specificity). Common fatal flaws for treatment trials included very high attrition (>40%), small sample size with high attrition and/or differential attrition, and very poor reporting limiting evaluation of risk of bias. We excluded poor-quality studies from this review.

Data Synthesis and Analysis

For diagnostic accuracy studies on screening for MCI or dementia (Key Question 2), our primary outcomes of interest were sensitivity and specificity at a given cut-point for the instrument. We present our synthesis of results in summary tables and figures organized by instrument type (according to length of administration) and separated by screening for dementia, MCI and dementia, or MCI only. When applicable and possible, we synthesized and reported the results for the most commonly used cut-point(s). We categorized these instruments as very brief

(administered in ≤5 minutes), brief (within 6 to 10 minutes), or self-administered. We relied on published administration times or administration times reported in the individual studies, although there is some variation in administration time based on the impairment of the individual (e.g., cognitive impairment, sensory impairment, depression).

We synthesized results around diagnostic accuracy (i.e., sensitivity and specificity) of instruments that were evaluated in more than one study. We reported the sensitivity and specificity for the most commonly accepted or reported cut-points, although cut-points varied according to the population characteristics (e.g., age, education) for some instruments, and in some cases, cut-point(s) were not reported. While we also extracted and/or calculated positive and negative predictive values, we did not focus on these measures because the prevalence of cognitive impairment varied widely across studies. We address the impact of underlying prevalence on positive and negative predictive values in the Discussion section to inform issues around the optimal age at which to start and stop screening. We synthesized results for test performance to detect 1) dementia, 2) MCI or dementia, and 3) MCI only (excludes people with dementia). We did not report test performance outcomes for the detection of dementia if the study removed persons with MCI from the study sample altogether because the sensitivity and specificity were not comparable with other studies that included the full sample. Additionally, this method of calculation was more similar to nested case-control diagnostic studies that we excluded from our review (only applied to three studies).[133-135] Test performance was either directly extracted from individual study results, calculated using study presented 2x2 tables, or calculated using the prevalence of cognitive impairment and the reported sensitivity and specificity (dementia, MCI, or dementia and MCI). We used SAS software (SAS Institute, Inc., Cary, NC) to generate 95% CIs. In general, we summarized ranges of sensitivity and specificity for each instrument, as we were unable to quantitatively pool the majority of the results given the limited number of studies per instrument, heterogeneity or lack of reporting around cut-points (and scoring), and in some cases, heterogeneity around populations and diagnostic criteria. We also used figures to visually display the diagnostic accuracy without producing summary estimates. We conducted quantitative synthesis of diagnostic screening studies if sufficient data were presented to determine test performance (sensitivity and specificity) in more than two similar studies. Similar studies needed to report similar outcomes (i.e., to detect dementia only, to detect MCI plus dementia, or to detect MCI only), be conducted in similar enough populations (i.e., based on underlying proportions of MCI and/or dementia), use similar scoring/cut-points, and apply a similar diagnostic criteria (e.g., Peterson criteria for amnestic MCI vs. suboptimal performance on Clinical Dementia Rating [CDR] scale). We could only conduct this quantitative synthesis for one instrument, the MMSE. For the analysis of dementia screening, cut-points were reported as being between 23 and 24 (23/24), between 24 and 25 (24/25), or simply 24 (some studies reported a cut-point of 24). We analyzed all studies reporting any of these three cut-points combined and then ran separate analyses for the three cut-points. We ran a bivariate model using the metandi procedure, which models sensitivity and specificity simultaneously, thus accounting for the correlation between these variables.[136] When the model failed for the 24/25 cut-point, likely due to sparse data, we analyzed sensitivity and specificity in separate random effect meta-analyses using the metan procedure. Similarly, since there were only three studies of MCI or dementia screening, we also ran separate random effects meta-analyses for sensitivity and specificity for this group.

For treatment trials (Key Questions 4, 5), we grouped interventions into four broad categories: 1) FDA-approved medications to treat AD (i.e., AChEIs and memantine); 2) other medications or dietary supplements (i.e., to treat VaD, NSAIDs, gonadal steroids, and vitamins); 3) nonpharmacologic interventions aimed primarily at the caregiver or caregiver-patient dyad; and 4) nonpharmacologic interventions aimed primarily at the patient, including: cognitive training, rehabilitation, and/or stimulation with or without motor skills training interventions; exercise interventions; multidisciplinary care interventions involving assessment and care coordination; and education-only interventions. Cognitive training interventions aim to enhance cognitive skills, most often memory and attention, through practice; cognitive rehabilitation aims to improve coping with cognitive deficits and preservation of remaining skills; and cognitive stimulation aims to enhance cognitive function through structured group discussions on various topics (e.g., current affairs, word association) to create both an optimal learning environment and social benefits of a group.[137] We synthesized results within each category (results as an entire category and by similar interventions within each category). We examined results and the association of key study characteristics on results and effect sizes on primary outcomes (when possible). These study characteristics included population characteristics (i.e., age, sex, severity of cognitive impairment, caregiver hours), setting characteristics (i.e., residential care or assisted living, country), intervention characteristics (i.e., intervention components, dosing/frequency or intensity), length of followup, and study quality.

Dementia can be characterized by progressive decline in three areas: cognition, global functioning, and physical functioning. For assessment of global cognitive function, the most commonly used measures in our included studies were the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)[138] and the MMSE. We used ADAS-cog as the primary measure. We used the MMSE when the ADAS-cog was not available. In the rare instance in which neither of these two measures was used, we accepted other measures of global cognitive functioning (e.g., Mattis Dementia Rating Scale). The ADAS-cog is a validated instrument that assesses memory, attention, orientation, language, and praxis. Scores range from 0 to 70, with higher scores signifying greater cognitive impairment, and a change of 4 points or more is considered clinically significant for patients with mild to moderate dementia.[139] The MMSE is a validated instrument that assesses memory, attention, orientation, language, and praxis. Scores range from 0 to 30, with lower scores signifying greater cognitive impairment, and a change of 3 points or more is generally considered to be clinically significant.[140] Assessment of global function was not commonly reported except in trials evaluating FDA-approved medications for AD. The most commonly used instrument in this body of literature is the Clinician-based Impression of Change plus caregiver input (CIBIC-plus).[141] With the CIBIC-plus, an experienced and independent clinician interviews the patient and a caregiver and rates the patient on a 7-point scale (1=very much better, 4=no change, 7=very much worse) in four areas: general, cognitive, behavioral, and ADLs. Any change in score is considered clinically significant. Global physical functioning was measured by a variety of different instruments capturing the patient's ability to complete basic ADLs (i.e., bathing, grooming, toileting, dressing, transferring, ambulating, and feeding)[142] and/or IADLs (i.e., shopping, managing transportation, driving, walking outdoors, climbing stairs, managing finances, doing housework or laundry, using the phone, managing medications, preparing meals, or holding a job).[143]

For each body of literature, we conducted qualitative syntheses for each of the commonly

reported outcomes, which varied by intervention type. While we also address less commonly reported outcomes, we primarily focus on the commonly reported outcomes due to the bias from selective reporting. For each body of literature, we created summary tables to capture the key study characteristics and sources of clinical heterogeneity (e.g., study quality, sample size, location, age, sex, baseline cognitive function/MMSE score, duration of followup), as well as the overall results for each included study. We conducted quantitative analyses on important patient outcomes reported in more than half of the included trials; most often this included global cognitive function. Pooled analyses were conducted for FDA-approved medications to treat AD and other medications and dietary supplements on global cognitive outcomes, caregiver interventions on caregiver burden and depression outcomes, and other nonpharmacologic interventions aimed at the patient on global and domain-specific (i.e., memory only) cognitive outcomes. Trials generally had limited duration of followup; summary tables focus on the longest duration of followup for each trial. For quantitative analyses, we focus on 12-month (i.e., 6 to 18 months) outcomes.

For continuous outcomes (i.e., global cognitive function, caregiver burden, caregiver depression), we analyzed a standardized effect size (Hedge g) based on the differences in change between groups from baseline to followup. For most trials, the Hedge g was calculated from mean change from baseline to followup in each group, along with an associated standard deviation, using standard formulae.[144] When given baseline and followup means and standard deviations (rather than change from baseline), we had to calculate a standard deviation of change, which required estimating the correlation between baseline and followup scores for each outcome. We used the following correlation estimates: global cognitive outcomes, 0.82 (intervention group) and 0.82 (control group); caregiver burden, 0.79 (intervention group) and 0.92 (control group); and depression, 0.72 (intervention group) and 0.75 (control group). These correlations were derived from included studies that reported both mean change (and standard deviation) and baseline and followup means (and standard deviations).[145,146] We used commonly accepted values to interpret the clinical significance of actual differences in means for specific outcome measures (i.e., ADAS-cog, MMSE), as well as commonly accepted values to interpret the clinical significance of standardized effect sizes. For global cognitive measures, an ADAS-cog change of 4 points or more or a MMSE change of 3 points or more are considered clinically important improvement in mild to moderate dementia.[94] For standardized effect sizes, standardized mean differences of 0.2 to less than 0.5 are considered small, 0.5 to less than 0.8 are medium, and 0.8 and above are large.[147]

In quantitative analyses with at least 10 trials, we used meta-regressions to explore heterogeneity in effect sizes. We examined key study characteristics, including: length of followup, study quality, year of publication, age, percent women, patient baseline MMSE score, and intervention characteristics (i.e., number of sessions offered as part of the intervention, total hours of contact with an interventionist, group sessions, one-on-one sessions, peer support, problem-solving training, communication training, stress management, supportive counseling, provision of dementia information, use of active techniques, intervention geared toward whole family, home safety assessment or information, direct patient care, care or case management, and total number of specified treatment components included in the intervention). We entered each of these predictors into a separate meta-regression model. We created forest plots with studies sorted by effect size for all analyses (regardless of number of included trials), using visual inspection to

examine if certain key characteristics may be associated with effect size. For caregiver interventions, we also examined effect size estimates separately for four different types of control groups: usual care in primary care in the United States; usual care outside the United States or in specialty clinics in the United States; usual care plus print materials, generic (nontailored) computer- or Web-based information, referral to support group or other community resources, and/or a single phone or in-person contact estimated to last 15 minutes or less, or attention control; and multiple contacts for caregiver or patient, or a single contact lasting more than 15 minutes.

We assessed the presence of statistical heterogeneity among the studies using standard chi-square tests and estimated the magnitude of heterogeneity using the I^2 statistic.[148] We also conducted analyses to determine prediction intervals, which provide an estimate of where 95 percent of newly conducted trials would fall, assuming the between-study variability in the included trials held for new trials.[144] The prediction intervals are not shown in our results but are mentioned in the Discussion section. We used a variety of approaches to examine whether pooled effects may have been biased due to small, imprecise studies having larger than expected effect sizes. We first performed tests of publication bias that examine whether the distribution of the effect sizes was symmetric with respect to effect precision using funnel plots, Egger's linear regression method, and Begg and Mazumdar's rank correlation test.[149] We also used a trim-and-fill procedure to look at the degree to which pooled estimates changed after the trim-and-fill procedure has adjusted the estimate for the potential effect of missing studies.[150] Finally, we ran a cumulative meta-analysis, entering studies in the order of the standard error of the effect estimate (which is highly related to sample size). We visually examined the resulting forest plot to see if the pooled effect increased as smaller studies were added to the analysis. We conducted these analyses of small study effects only in analyses that included at least 10 trials.[151]

We used Stata 11.2 (StataCorp LP, College Station, TX) for all statistical analyses unless otherwise noted.

USPSTF Involvement

The authors worked with four USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and key questions and to resolve issues around scope for the final evidence synthesis. This research was funded by AHRQ under a contract to support the work of the USPSTF. AHRQ staff provided oversight for the project, reviewed the draft report, and assisted in external review of the draft evidence synthesis.

Chapter 3. Results

Key Questions 1–3: Overall Summary of Results for Screening for Cognitive Impairment

No trials examined the direct effect of screening for cognitive impairment on important patient outcomes, including decisionmaking outcomes. We identified 55 studies that address the diagnostic accuracy of brief screening instruments. The majority of these studies were not included in the prior USPSTF review. In order to be included in our review, the study had to assess the performance of an instrument that could be administered in less than 10 minutes or self-administered in less than 20 minutes. To facilitate discussion of results, we categorized these instruments as very brief (administered in ≤5 minutes), brief (within 6 to 10 minutes), or self-administered. We included 29 very brief instruments, 19 brief instruments, and 5 self-administered instruments (**Table 1**). All of these instruments can be administered and scored with minimal training.

Despite a very large body of evidence examining cognitive screening instruments, most instruments have only been studied in a handful of well-designed diagnostic accuracy studies in primary care–relevant populations (**Tables 2–10**). The best-studied instrument remains the MMSE, which has a relatively long administration time compared with other screening instruments included in this review. For the MMSE, the most commonly reported cut-points were 23/24 and 24/25, although higher and lower cut-points were evaluated in various studies. Pooled estimates across 14 studies (n=10,185) resulted in 88.3 percent sensitivity (95% CI, 81.3% to 92.9%) and 86.2 percent specificity (95% CI, 81.8% to 89.7%) for a cut-point of 23/24 or 24/25. Studies in populations with low levels of education (majority with primary school education or less) used lower cut-points. Test performance to detect MCI was based on a much smaller body of literature (k=15; n=5,758). Studies using higher cut-points to detect MCI did not have better sensitivity or specificity. Other instruments with more limited evidence include the CDT, Mini-Cog, MIS, AMT, SPMSQ, Free and Cued Selective Reminding Test (FCSRT), 7-Minute Screen, Telephone Interview for Cognitive Status (TICS), and IQCODE. The CDT also has several studies to support its use (k=7; n=2,509); however, it has a much wider range of sensitivity and specificity (67% to 97.9% and 69% to 94.2%, respectively) and the optimal cut-point is unclear from the body of literature we examined. The Mini-Cog, based on a smaller body of literature (k=4; n=1,570), likely has better sensitivity than the CDT alone (76% to 100%), but with a possible tradeoff of lower specificity (54% to 85.2%). For MCI, the CDT (k=4; n= 4,191) and Mini-Cog (k=3; n=1,092) have much lower sensitivity. Although the MIS (k=5; n=1,971) can have relatively good test performance to screen for dementia (sensitivity, 43% to 86%; specificity, 93% to 97%), the two best-quality studies (n=948) showed very low sensitivity (~40%). Likewise, the AMT (k=4; n=824) can have relatively good test performance to screen for dementia (sensitivity, 42% to 100%; specificity, 83% to 95.4%), but one fair-quality study (n=289) had very low sensitivity (42%) and no studies were conducted in the United States. The SPMSQ (k=4; n=1,057), FCSRT (k=2; n=734), 7MS (k=2; n=553), and TICS (k=2; n=677) also have reasonable test performance, but based on a very limited number of studies. If a self-administered or informant-based screening tool is desired, the IQCODE may be a reasonable option to screen for either dementia (k=5; n=1,108; sensitivity, 75% to 87.6%; specificity, 65%

to 91.1%) or MCI (k=4; n=975; sensitivity, 71.1% to 82.6%; specificity, 69.0% to 83.0%). However, for all these other instruments, there is much more limited evidence to support their use, with limited reproducibility in primary care–relevant populations and unknown optimal cut-points for each instrument. The AMT, SPMSQ, FCSRT, 7-Minute Screen, and TICS have very limited evidence in English. The AMT, MIS, SPMSQ, and TICS have no writing or drawing component and therefore can be administered to visually impaired individuals. Other instruments (i.e., 6-Item Screener, Visual Association Test [VAT], GPCOG, ADLs/IADLs, Benton's Orientation Test, Delayed Recall Test, and Short Concord Informant Dementia Scale for dementia; AD8, SLUMS, and Computer Assessment of Mild Cognitive Impairment [CAMCI] for MCI) appear promising (>80% sensitivity and specificity), but their test performance has not been reproduced in other primary care–relevant populations. No studies directly address the adverse psychological effects of screening or adverse effects from false-positive or false-negative testing. One fair-quality study found that approximately half of the older adults who screened positive for cognitive impairment refused to complete a formal diagnostic workup.

Key Question 1. Does Screening for Cognitive Impairment in Community-Dwelling Older Adults in Primary Care–Relevant Settings Improve Decisionmaking, Patient, Family/Caregiver, or Societal Outcomes?

We found no trials that directly assessed whether screening for cognitive impairment in primary care could affect decisionmaking, health (patient or caregiver), or societal outcomes. No trials have been designed to assess whether screening for cognitive impairment changes patient or clinical decisionmaking or if screening improves patient, caregiver, or societal outcomes in addition to the standard of care, which is primarily testing for cognitive impairment based on clinical observation or other mechanisms of case-finding.

Key Question 2. What Is the Test Performance of Screening Instruments to Detect Cognitive Impairment in Community-Dwelling Older Adult Primary Care Patients?

Screening for Dementia

We found 41 studies that addressed the diagnostic accuracy of very brief and brief screening instruments that could be administered in primary care (**Appendix D Tables 1** and **2**) and seven studies that addressed instruments that could be self-administered (**Appendix D Table 3**).

Our included studies considered a broad range of participants relevant to older adult primary care populations and a wide variety of different screening instruments (**Tables 2–10**). Overall, study participants were community-dwelling older adults selected from the community or primary care practices. Two studies explicitly included people in assisted living or residential care facilities.[152,153] Almost all studies had a majority of women participants, but studies varied in the mean age (range of means, 69 to 95 years) and prevalence of dementia (range of prevalence, 1.2% to 47.1%). Education was not always reported. If education was reported, it was often

reported differently across studies. In general, however, most study participants had at least some high school education. In 12 studies (none of which were conducted in the United States), most of the participants had less than a high school education.[154-165] The study population in six of these studies had very low levels of education (i.e., no formal education or only primary school).[160,160,162-165] The most commonly evaluated screening instruments included (most to least common, instruments only evaluated once are not listed here): MMSE (k=25; n=12,348), CDT (k=7; n=2,509), verbal/category fluency tests (k=6; n=2,083), short or full IQCODE (k=5; n=1,108), MIS (k=4; n=1,671; k=1 for MIS-T; n=300), Mini-Cog (k=4; n=1,570), AMT (k=4; n=824), SPMSQ (k=4; n=1,057), Mental Status Questionnaire (MSQ) (k=2; n=522), FCSRT (k=2; n=734), 7-Minute Screen (k=2; n=553), and TICS (k=2; n=677).

For inclusion in this review, diagnostic accuracy studies were required to minimize selection bias (i.e., distorted selection of participants with case-control study design) and evaluate index tests against a true diagnostic reference standard, rather than other screening instruments. Only four studies were good quality; most were fair quality, with a range in risk of biases, the most common being partial verification (only a subset of participants whose screening test was negative received reference standard), unclear or lack of independence of application or interpretation of index test (screening) and reference standard, selection bias with stratified sampling or sampling of volunteers only, and unclear spectrum of patients due to poor reporting of how study population was derived or percent of/reasons for attrition. All studies had to apply a diagnostic reference standard. For dementia, the most common reference standard was DSM-III or DSM-IV or National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, although others used AGECAT or Cambridge Mental Disorders of the Elderly Examination (CAMDEX). Many studies did not explicitly mention the specific criteria they used to diagnose dementia. No studies used the most recent National Institute on Aging-Alzheimer's Association criteria.[166] Studies generally did not specify the type or etiology of dementia. Most included studies used a combination of history, examination, neuropsychological testing, and/or expert consensus to determine the formal diagnosis.

Very Brief Instruments (Table 2, Figure 2)

CDT. Two good-quality and five fair-quality studies evaluated the performance of the CDT.[161, 162,167-171] While mean age and percent women in each study did not vary widely, there was large variation in prevalence of dementia. In the fair-quality studies, the proportion of people with dementia ranged from 5 to 11.5 percent. The proportions, however, were much higher in the good-quality studies (17.6% and 47.1%). In general, the range of sensitivity and specificity for the CDT across six studies (n=2,170) that reported this information was 67 to 97.9 percent (range 95% CI, 39 to 100) sensitivity and 69 to 94.2 percent (range 95% CI, 54 to 97.1) specificity.[161,162,167-169,171] The highest estimate (94.2%) for specificity comes from the good-quality study, conducted much earlier than the other studies, with an unusually high prevalence of dementia in this sample.[171] Two studies with the highest sensitivity estimates (89.5% and 97.9%) were both conducted in populations with on average low levels of education.[161,162] It is unclear if the education level or another study characteristic particular to these two studies affected the instrument's sensitivity. The lack of reporting on how each CDT was scored, however, presents a major limitation for comparing estimates across studies. There are also

multiple scoring methods for interpreting the CDT (each with varying degrees of complexity). Currently, there is no consensus on the best method, and only two of these six studies report the cut-points used (and used different cut-points).[168,169] In general, while the CDT can have reasonable sensitivity and specificity, the 95% CI across studies varies widely and the diagnostic accuracy will vary with choice of scoring method and cut-points.

Mini-Cog. The Mini-Cog instrument includes the CDT plus a three-item word recall test. One good-quality and three fair-quality studies evaluated the Mini-Cog,[152,161,172,173] one of which was administered in German.[161] While the patients' mean age was about 79 years, the prevalence of dementia varied greatly across the four studies (range, 3.3% to 40.2%), which suggests important population differences. Across the four studies (n=1,570), sensitivity ranged from 76 to 100 percent (range 95% CI, 54 to 100) and specificity ranged from 54 to 85.2 percent (range 95% CI, 43 to 88.4).[152,161,172,173] The best test performance was found in a study conducted in a population with a fairly low level of education.[161] One study with a particularly low specificity was conducted in a residential care facility in a population with a very high proportion of people with dementia.[152] It is unclear, however, if the differences in test performance are due to education, setting, or underlying prevalence of dementia, or if these differences are due to some other study-specific characteristic. Again, while lack of reporting and differences in cut-points limits the interpretation of results, it appears that the Mini-Cog has a better sensitivity than the CDT alone, although this increased sensitivity comes with a tradeoff of decreased specificity. However, it is difficult to assess whether adding the three-item word recall test improves sensitivity and specificity because of differences across studies in ages and proportion of people with dementia in the populations evaluated, and not knowing the differences in how the CDT was scored.

MIS. The MIS is a brief four-item delayed free and cued recall memory impairment test. Although related, it is different than the FCSRT (see the Brief Instruments section). Two good- and three fair-quality studies evaluate the MIS,[168,173-176] one of which evaluates the MIS by telephone (MIS-T).[176] All these studies had a similar mean age, 78 to 79 years, and levels of education; however, the proportion of people with dementia ranged from 3.3 to 17.6 percent. One good-quality study had a majority of men (92.9%), which is quite different than most other studies included in this review. Across the five studies (n=1,971), sensitivity ranged from 43 to 86 percent (range 95% CI, 24 to 96) and specificity ranged from 93 to 97 percent (range 95% CI, 56 to 100) at a cut-point of 4. One of these studies (n=300), which evaluated the MIS-T, had a similar test performance to the MIS evaluated in the other studies. Overall, sensitivity for the MIS varies widely; the point estimates for sensitivity were only 43 and 49 percent in the two best-quality studies.

MSQ and SPMSQ. The SPMSQ was derived from the MSQ, with a few added questions; both of these instruments have a possible score of 10 errors. Two fair-quality studies evaluated both the MSQ and the SPMSQ,[177,178] and two additional fair-quality studies evaluated the SPMSQ.[155,162] Only one of these studies evaluated the MSQ or SPMSQ in English; the other studies evaluated the performance of the SPMSQ in Spanish, Finnish, and Dutch. Across these studies, the mean age and proportion of women were not well reported. The percentage with dementia in the study populations ranged from 2.5 to 16.4 percent. Across the four studies (n=1,057), sensitivity for the SPMSQ ranged from 92.3 to 100 percent (range 95% CI, 29 to 100) and specificity ranged from 83.5 to 100 percent (range 95% CI, 76 to 100).[155,162,177,178] In the two studies that evaluated both

the SPMSQ and MSQ (n=522), both instruments had similar diagnostic accuracy.[177,178] Although the cut-points were not specified in two of the four studies, overall the SPMSQ seems to have reasonable performance, albeit with a wide range in 95% CIs.

Verbal Fluency Tests. Verbal fluency tests can be category (measures language ability) or letter fluency tests (measures executive functioning) that assess the ability to name as many items in a category (e.g., animals, fruits, first names) or starting with a specific letter in 1 minute. One good- and five fair-quality studies evaluated verbal fluency tests.[161,162,168,170,176,179] Two of the studies evaluated tests in German[161,179] and one in Spanish.[162] Mean age was similar across studies and ranged from 76.6 to 82.4 years. The proportion of women ranged from 51.7 to 83 percent. Dementia prevalence ranged from 5 to 17.6 percent. Although the cut-points used in each of the studies varied and was not reported in one study, sensitivity and specificity overlapped regardless of chosen cut-point. In three of the studies (n=1,041), sensitivity ranged from 37 to 89.5 percent (range 95% CI, 19 to 100) and specificity ranged from 62 to 97 percent (range 95% CI, 48 to 99) for a cut-point of 12 or 13.[161,168,176] Again, the highest test performance came from one German study in which the population screened had low levels of education.[161] In three of the studies (n=905), sensitivity ranged from 57 to 88 percent (range 95% CI, 35 to 100) and specificity ranged from 43 to 94 percent (range 95% CI, 33 to 97) for a cut-point of 14 or 15.[168,176,179] Verbal fluency tests have a wide range of sensitivity and specificity, with likely unacceptably low sensitivity for lower thresholds and low specificity for higher cut-points.

Brief Instruments (Table 3, Figure 3)

AMT. The AMT is a 10-item instrument that was introduced in 1972 and is not commonly used in the United States.[180] Four fair-quality studies evaluated the AMT in different populations and languages (English, Dutch, and South Asian languages), none of which were conducted in the United States.[154,178,181,182] The earliest and largest study (n=358) was conducted in Holland and had a sensitivity and specificity of 92.3 percent (95% CI, 64 to 99.8) and 95.4 percent (95% CI, 92.6 to 97.3), respectively, for a cut-point of 7/8.[178] A subsequent study (n=269) in Australia, however, found a much lower sensitivity of 42 percent (95% CI, 31 to 53), with similar specificity of 93 percent (95% CI, 89 to 96) for the same cut-point.[154] The prevalence of dementia in this population was much higher at 29 percent compared with 3.6 percent in the Dutch study. Two smaller studies (n=194) in ethnic minorities in the United Kingdom suggest that the AMT can have relatively high sensitivity and specificity. The 95% CIs are very wide, however, and the optimal choice of cut-point may vary by language/culture or education.[181,182] These two studies were also conducted in slightly younger populations (mean age, 69 years) than most included studies. Overall, the AMT has limited reproducibility in similar primary care–relevant populations and it is unclear how applicable these populations are to U.S. primary care populations.

FCSRT. Only two studies evaluated the FCSRT.[162,168] One good-quality study conducted by Grober and colleagues (n=318) found that the FCSRT had a sensitivity of 86 percent (95% CI, 41 to 100) and specificity of 73 percent (95% CI, 56 to 96) at a cut-point of 25 in a patient population with a mean age of 78.7 years and 17.6 percent underlying dementia.[168] A fair-quality study (n=416) conducted in a Spanish population found that a modified FCSRT (details and cut-point unknown) had high sensitivity (100% [95% CI, 92.6 to 100]) and specificity (87.2% [95%

CI, 83.4 to 90.5]). This population had similar age, sex, and proportion of patients with dementia but much lower education levels than the Grober studies. The FCSRT has had limited validation in a primary care–relevant population, and CIs around sensitivity and specificity are wide.

7-Minute Screen. The 7-Minute Screen is a combination of the Benton Temporal Orientation Test, an abbreviated version of the Enhanced Cued Recall test, the CDT, and the animal verbal fluency test. Only two fair-quality studies evaluated the 7-Minute Screen,[162,183] one of which was conducted in Spanish.[162] These two studies (n=553) included similar aged populations, majority women, and proportion of people with dementia (8.0% and 11.5%). Sensitivity was 100 percent (range 95% CI, 71.5 to 100) and specificity ranged from 95.1 to 100 percent (range 95% CI, 86.8 to 100). Due to limitations in the individual studies, however, the optimal cut-point is not known. Evidence to support the use of the 7-Minute Screen in primary care is very limited (limited number of studies, range and sensitivity, and unknown optimal cut-point).

TICS. The TICS is an 11-item instrument that can be administered by phone or in person, does not require vision, and therefore can be used in visually impaired individuals. Only two fair-quality studies evaluated the TICS.[176,184] These two studies were similar in mean age and proportion of women and the prevalence of underlying dementia was 9 and 14.1 percent. In these two studies (n=677), sensitivity ranged from 74 to 88 percent (range 95% CI, 54 to 96) and specificity from 86 to 87 percent (range 95% CI, 81 to 91). The two studies, however, used very different cut-points (28 and 22). At present, the TICS has very limited evidence (limited number of studies and unknown optimal cut-point).

MMSE. The MMSE is by far the most well-studied, and arguably most well-known, instrument to screen for dementia. It is a 30-point instrument with 11 items. In diagnostic studies, the MMSE was often included as a comparator with other index tests and was not the primary instrument being evaluated. Nonetheless, 25 fair-quality studies evaluated the MMSE in primary care–relevant populations.[152-154,157-160,163-165,169,170,177-179,181,182,185-192] Researchers have studied the MMSE in multiple languages (English, Spanish, French, Swedish, German, Dutch, Korean, Cantonese, and South Asian languages) across a range of older and very old adults (mean age range, 69 to 95 years) and a wide range of dementia prevalence (1.2% to 38%). Although it is well accepted that the MMSE has different norms by age and education (and ethnicity[193]), there is no universally accepted cut-point based on age and education level.[19] The most commonly reported cut-points were 23/24 and 24/25, although higher and lower cut-points were evaluated in various studies. Pooled estimates across 14 studies (n=10,185) resulted in 88.3 percent sensitivity (95% CI, 81.3 to 92.9) and 86.2 percent specificity (95% CI, 81.8 to 89.7) for a cut-point of 23/24 or 24/25. For a cut-point of 23/24 (k=5; n=3,190), the pooled sensitivity was 85.4 percent (95% CI, 79.1 to 90.0) and specificity was 90.2 percent (95% CI, 86.0 to 93.3). For a cut-point of 24/25 (k=5; n=1,562), the pooled sensitivity was 87.6 percent (95% CI, 81.6 to 93.7) and specificity was 84.1 percent (95% CI, 76.4 to 91.8). The four remaining studies only reported a cut-point of 24 (n=4,866). It is unclear if these studies considered a score of 24 as normal or abnormal. Three studies, two conducted in Spain and the other in South Korea, used much lower cut-points and found overlapping sensitivities similar to those in other studies with higher thresholds.[160,163,165] Despite these similarities, however, these studies were conducted in populations with much lower education levels. Although sensitivity and specificity of the MMSE

likely varies depending on the individual's age and education, a large body of literature suggests a general cut-point of 23/24 or 24/25 could be appropriate for most primary care populations.

Self-Administered Instruments (Table 4, Figure 4)

IQCODE. The full version of the IQCODE includes 26 items and the short version includes 16 items. The questionnaire can be self-administered to the patient's informant (i.e., caregiver, family, close friend). Based on similar performance (correlation) between the two instruments, the developers of the instrument recommend using the short version with a cut-point of 3.44 or greater.[194] One good-quality study evaluated the short IQCODE,[168] one fair-quality study evaluated both the short and long form,[188] and three fair-quality studies evaluated the long/full IQCODE.[160,165,195] Two of these studies were conducted in Spanish in populations with low levels of education. The cut-points across the studies varied and every study used a different threshold. Despite this heterogeneity, the short IQCODE had a sensitivity of 75 to 81 percent (range 95% CI, 41 to 100) for dementia and specificity from 68 to 80 percent (range 95% CI, 59 to 100) for a cut-point around 3.3 in two studies (n=461).[168,188] The full version of the IQCODE had a sensitivity of 79 to 83 percent (range 95% CI, 48 to 98) and specificity from 65 to 90 percent (range 95% CI, not reported to 95) for a cut-point around 3.3 in two studies (n=400).[165, 188] In two other studies (n=390) using higher cut-points, sensitivity and specificity overlapped with those from other studies that used lower thresholds in populations with similar age and underlying dementia.[160,195] If an informant-based screening tool is desired, the short or full IQCODE is the most well-studied in a primary care–relevant population. It is important to note, however, that the CIs are somewhat wide, and the instrument developer's suggested cut-point was not used/reported in these included studies.

Other Instruments

Sixteen other instruments were each only evaluated in a single study. Promising very brief instruments, based on high sensitivity and specificity (>80%), include: 6-Item Screener, VAT, GPCOG, and functional ability/activity instruments (e.g., ADLs, IADLs) (**Appendix D Table 1**); brief instruments include Benton's Orientation Test and the Delayed Recall Test (10 words, 10 minutes) (**Appendix D Table 2**); and self-administered instruments include the Short Concord Informant Dementia Scale (adapted from IQCODE) (**Appendix D Table 3**). One instrument, the GPCOG, was specifically designed for use in primary care.[154] Without reproduction/replication of diagnostic accuracy in well-conducted diagnostic studies in populations relevant to outpatient primary care, these instruments cannot be suggested in place of more well-studied instruments.

Screening for MCI

We found 27 studies designed to assess the diagnostic accuracy of a smaller subset of screening instruments (22 instruments) to detect MCI in primary care–relevant populations (**Tables 5–10**). Fifteen of these studies estimated (or allowed us to estimate) the diagnostic accuracy for MCI alone (excluded patients with dementia), while 16 of these studies estimated (or allowed us to estimate) the instrument's accuracy of detecting either MCI or dementia. These two estimates of diagnostic accuracy (i.e., detection of MCI vs. detection of MCI plus dementia) may not be comparable, as sensitivity may be relatively lower in populations that exclude dementia patients

(because instrument likely has better discrimination in patients with a higher level of cognitive impairment; in other words, we would expect a higher number of false-negatives in the MCI vs. dementia group). As such, we present these data separately.

Although a much smaller body of literature than that of screening for dementia, this evidence base to detect MCI is a new and growing body of literature. In fact, almost all the studies of diagnostic accuracy were published during the past 10 years. All studies included populations to approximate those seen in primary care, most of which were community-dwelling older adults. Only two studies explicitly included patients in assisted living or residential care facilities.[153,196] Almost all studies had a majority of women participants, but studies varied in the mean age (range of means, 70 to 83 years) and the prevalence of MCI (range of prevalence, 5% to 84%). Level of education was not reported in several studies. When reported, the education level varied. In the majority of studies, participants had at least a high school education. In eight studies not conducted in the United States, however, participants had on average a primary school education or less.[133,160,163,164,196-199]

The most commonly evaluated screening instruments to detect MCI were (most to least common): MMSE (k=15; n=5,758), IQCODE (k=4; n=975), CDT (k=4; n=4,191), Mini-Cog (k=3; n=1,092), TICS (k=3; n=568), and MoCA (k=2; n=251). Other commonly known/used instruments that were evaluated in only one study include the AD8, MIS, and SLUMS.

There were only four good-quality studies;[163,173,200,201] the remaining fair-quality studies had similar quality concerns as those summarized previously. However, there was more variation in which diagnostic criteria were applied for MCI. The majority of studies applied the Petersen criteria (or "in the spirit" of the Petersen criteria), the international working definition by Winblad and colleagues, or suboptimal performance on cognitive testing (e.g., between 1 to 2 SDs below norm, CDR score of 0.5) without evidence of functional limitations. The Petersen criteria define amnestic MCI, thought to be a prodromal stage of AD, focusing on memory impairment, whether in isolation or in combination with other cognitive domains. In contrast, the Winblad criteria include both amnestic and nonamnestic types of MCI. The CDR is heavily weighted toward testing memory and therefore is more suited to detecting amnestic MCI, but is also inclusive of amnestic and nonamnestic types of MCI. A few studies, however, did not give details (e.g., used judgment, did not meet DSM-III or DSM-IV criteria for dementia). Again, most studies used a combination of history, examination, neuropsychological testing, and/or expert consensus to determine the formal diagnosis. The variation in diagnostic criteria limits comparability of diagnostic estimates across studies and is an important contributor of heterogeneity (along with population differences) leading to variation in screening test performance.

Very Brief Instruments (Tables 5 and 9, Figure 5)

CDT. Four fair-quality studies evaluated the CDT in English, German, and Korean.[196,198,199,202] These studies did not include people with dementia. These studies evaluated the performance of the CDT in different populations, using different cut-points and different diagnostic criteria for MCI. The largest study (n=3,198) was performed in an older, mostly female, poorly educated German population (mean age, 80.1 years). This study used two different reference criteria for

MCI. Using the Peterson-like criteria, however, the prevalence of MCI was only 15 percent. Using modified criteria (did not require subjective cognitive impairment), the prevalence was 24.6 percent. Regardless of the diagnostic criteria, the sensitivity and specificity of the CDT was only around 60 percent. Another study from Germany (n=428), using the Winblad criteria, found a range of sensitivity of 48 to 76 percent and specificity of 49 to 79 percent regardless of scoring methods. This study recruited institutionalized (only around 11%) along with community-dwelling older adults, had a mean age of 83 years, and 64 percent of the sample had low education.[196] Another study, from South Korea (n=465), was performed in a younger population that was also predominantly comprised of women with lower levels of education.[199] Using the Peterson criteria, this study found that about 48 percent of the population had MCI and that the sensitivity was similarly low (range, 40.7% to 56.4%, depending on scoring method). This study also showed that the test performance varied depending on which scoring system the study used. Finally, the estimated sensitivity was higher (85%) in a smaller study (n=100), although the specificity was poor (44%).[202] In this study, however, investigators used 1 SD as the cut-point for the instrument, and the diagnostic criteria for MCI was based on 1 SD below the (age adjusted) normative mean on the Dementia Rating Scale. Across four very different studies (n=4,191), the CDT appears to have worse sensitivity or specificity to detect MCI than to detect dementia using different cut-points.

Mini-Cog (Figure 5). Two studies evaluated the diagnostic performance of the Mini-Cog to detect MCI or dementia.[172,173] One good-quality study (n=630) by Holsinger and colleagues conducted in a predominantly male population from a U.S. Department of Veterans Affairs (VA) setting with a low prevalence of dementia (3.3%) found a very low sensitivity of the instrument to detect MCI or dementia.[173] A smaller fair-quality study (n=371) by Borson and colleagues, however, used the same cut-point and found a much higher sensitivity of 84 percent (95% CI, 78.6 to 88.5) and specificity of 87.9 percent (95% CI, 81.3 to 92.8).[172] Although the overall prevalence of cognitive impairment was similar, the relative proportion of people with dementia versus MCI was much higher in the smaller study, likely resulting in a higher estimate of both sensitivity and specificity. Both studies used different diagnostic criteria for MCI. The study conducted by Borson and colleagues showed adequate test performance using a CDR score of 0.5 to define MCI.[172] One fair-quality study evaluated the performance of the Mini-Cog to detect MCI alone in an assisted living or residential care population.[152] This small study (n=91) estimated a very low sensitivity (50%) in this population, in which about 90 percent of residents had either MCI or dementia. Three very different studies (n=1,092) that used different definitions of MCI and different cut-points found different estimates of sensitivity to detect MCI plus or minus dementia.

Brief Instruments (Tables 6 and 9, Figure 6)

TICS-M. Two fair-quality studies evaluated the TICS-M to detect MCI and dementia.[184,203] One fair-quality study evaluated the TICS-M to detect MCI alone (excluding dementia patients).[204] These three studies each found different optimal cut-points. The largest study (n=377) had a mean age of 81.4 years, with 18 percent of people with MCI.[184] This study used the Mayo clinic criteria and found an optimal cut-point of 26 to detect either MCI or dementia, with a sensitivity and specificity of 73 percent (95% CI, 64 to 80) and 77 percent (95% CI, 71 to 82), respectively. In another study (n=120) conducted in French, while the age and prevalence were similar, the

optimal cut-point was higher at 31.[203] This study found that a lower cut-point of 27 had an unacceptably low specificity (46% [95% CI, 35 to 56]) and a higher cut-point of 34 had an unacceptably low sensitivity (47% [95% CI, 28 to 66]). Another small study (n=71) found the optimal cut-point to detect MCI (excluding patients with dementia) was 34, with lower cut-points of 31 and 26 to have low estimates of sensitivity (47.1% and 17%, respectively).[204] Three small studies with different populations that used different definitions of MCI arrived at widely varied estimates for sensitivity and specificity.

MMSE. The MMSE was the most studied instrument used to detect MCI. Two good- and 13 fair-quality studies examined the diagnostic accuracy of the MMSE to detect MCI plus or minus dementia.[134,152,153,159,160,163,164,185,186,188,197,200,202,203,205] Unfortunately, only 10 of the 15 studies reported sensitivity and specificity or provided sufficient data to allow us to calculate sensitivity and specificity.[134,152,153,160,163,185,186,200,202,205] These 10 studies used different definitions of MCI, had different proportions of underlying MCI and dementia, and used different cut-points. In three studies (n=1,235) with high prevalence of MCI (>40%), sensitivity ranged from 45 to 60 percent (range 95% CI, 36 to 74) and specificity ranged from 65 to 90 percent (range 95% CI, 56 to 99) to detect MCI (excluding people with dementia) using a cut-point of 27 or 28.[134,152,200] Another study conducted in residential care with a high proportion of people with cognitive impairment found that using a similar cut-point of 27 resulted in sensitivity of 71 percent (95% CI, 48 to 89) and specificity of 90 percent (95% CI, 77 to 97) to detect either MCI or dementia. Sensitivity ranged from 53 to 77 percent (range 95% CI, 43 to 85) in three other studies (n=1,544) with a range of prevalence of MCI and dementia (12.6% to 56.3%), and specificity ranged from 70 to 92 percent (range 95% CI, 58 to 99) using a cut-point of 23 or 24.[160,185,186] Another study (n=701) examined test performance using different cut-points in different ethnic groups.[205] The overall prevalence of MCI and dementia was 42.5 percent. The CIs for both the sensitivity and specificity of the MMSE overlapped when using a cut-point of 26 for whites, 25 for Latinos, and 23 for blacks. One small study (n=235) conducted in South Korea found a slightly better sensitivity, with an expected tradeoff in lower specificity, using a lower cut-point of 21.[163] This lower cut-point was likely chosen based on the low levels of education in this population. Among a limited subset of studies that reported sensitivity and specificity, a cut-point of 27 or 28 had a low (and widely ranging) sensitivity to detect MCI, and a cut-point of 23 or 24 appears to have a better sensitivity and specificity to detect MCI and dementia than most other screening instruments, albeit still less than optimal.

MoCA. The MoCA was specifically designed to detect MCI. One fair-quality[133] and one good-quality study[201] assessed the test performance of the MoCA to detect MCI (excluding people with dementia). Both of these studies used the Petersen criteria for MCI. One study was conducted in South Korea, with a mean age of 70 years, and had a prevalence of MCI of 24 percent. The other study was conducted in an older population (mean age, 76 years) in the United Kingdom and had a prevalence of MCI of 20 percent. Using a cut-point of 25/26, sensitivity and specificity ranged from 80 to 100 percent (range of 95% CI, 56.3 to 100) and 50 to 76 percent (range of 95% CI, 41 to 84.9), respectively.

Self-Administered Instruments (Tables 7 and 10, Figure 7)

IQCODE. Four fair-quality studies evaluated the short or full version of the IQCODE.[135,160,188,195]

Only three of these four studies presented results on the sensitivity and specificity of these instruments.[135,160,195] In two studies (n=390), the full version of the IQCODE using similar cut-points of around 3.3 had differing sensitivity and specificity, ranging from 71 to 83 percent (95% CI, 60.6 to not reported) and 74.3 to 83 percent (95% CI, 62.4 to not reported), respectively, to detect MCI or dementia.[160,195] These two studies, however, had different underlying prevalence of MCI and used different criteria to define MCI. The third study (n=441) found that the short version of the IQCODE using a cut-point of 3 had a sensitivity of 74.8 percent (95% CI, 67.7 to 80.7) and specificity of 69.0 percent (95% CI, 63.1 to 74.7) to detect MCI (excluding people with dementia).[135] These patients, however, were generally older (mean age, 80.3 years) and had a higher underlying prevalence of cognitive impairment (31.8% with dementia, 28.6% with MCI). Across three different studies, the IQCODE had relatively low sensitivity for detecting MCI.

Other Instruments

Seventeen other instruments were evaluated in our included studies; however, each instrument was only evaluated in a single study. Four instruments appear promising given their relatively high sensitivity and specificity compared with other instruments: AD8, abbreviated Fuld Object Memory Evaluation (FOME), SLUMS, and CAMCI. Only the CAMCI was specifically designed to detect MCI. However, currently there is no replication of the test performance for these instruments in adequately-conducted diagnostic accuracy studies in populations similar to those in primary care.

Key Question 3. What Are the Harms of Screening for Cognitive Impairment?

Screening for cognitive impairment may have direct or indirect harms from the diagnostic inaccuracy of screening (false-positives and false-negatives). We found no studies that directly addressed the adverse psychological effects from screening, adverse effects from unnecessary diagnostic testing (workup for false-positives), adverse effects from labeling or treating someone with dementia without diagnostic testing (false-positives without appropriate followup), or adverse effects from missed or delayed diagnosis (false-negatives).

We found only one fair-quality study that directly commented on the potential harms of screening for cognitive impairment in primary care.[206,207] This study found that approximately half (207/434) of older adults who screened positive for cognitive impairment refused to complete a formal diagnostic workup for dementia. This study was conducted in multiple urban, low-income primary care practices in the United States. Authors found that older patients and patients with higher screening scores were more likely to refuse further assessment.[207] While this study did not measure or report psychological harms of testing, the high refusal rate for diagnostic workup of screen-positive results may suggest that older adults have concerns about subsequent (yet necessary) diagnostic testing. Notably, the refusal for screening was low (233/3,573). Findings from this study may not be widely applicable to many U.S. practices, as two thirds of the study population were black women. In addition, diagnostic followup was offered by researchers, as opposed to the participant's primary care provider.

Key Questions 4, 5: Overall Summary of Results for Treatment and Management of Cognitive Impairment

We identified one systematic review and 131 studies that addressed the treatment or management of mild to moderate dementia or MCI (or mixed populations that included people with MCI or early-stage dementia). We discuss the benefits and harms of each type of intervention separately due to the broad range of interventions we examined. This review covers pharmacological interventions, including FDA-approved medications to treat patients with AD for the purpose of preventing cognitive decline (i.e., donepezil, galantamine, rivastigmine, tacrine, and memantine) (**Tables 11** and **12**); medications primarily aimed at cardiovascular risk reduction for treatment of VaD, including antiplatelet medications and HMG-CoA reductase inhibitors (**Table 13**); NSAIDs (**Table 13**); gonadal steroids (estrogen, progesterone, and testosterone) (**Table 13**); and dietary supplements (i.e., vitamins, minerals, antioxidants) (**Table 13**). This review covers nonpharmacologic interventions, including interventions aimed primarily at the caregiver or patient-caregiver dyad (**Table 14**) and those aimed primarily at the patient (i.e., cognitive training, rehabilitation, and/or stimulation with or without motor skills training interventions; exercise interventions; multidisciplinary care interventions involving assessment and care coordination; and education-only interventions) (**Table 15**).

Overall, based on 54 fair- to good-quality trials (n=19,384) that evaluated AChEIs (i.e., donepezil [k=24; n=7,552], galantamine [k=12; n=6,008], rivastigmine [k=12; n=4,829], tacrine [k=6; n=994]) that are FDA-approved for use in people with mild to moderate AD, this class of medications can improve global cognitive function in the short-term. The magnitude of these changes is small, at approximately 1- to 3-points change on the ADAS-cog. The majority of available evidence comes from trials in people with moderate (as opposed to mild) AD and followup was limited to 6 months. The average effect of these changes may not be clinically meaningful using commonly accepted values to interpret the clinical importance of these changes. On average, rivastigmine appears to have greater benefit than donepezil or galantamine on global cognitive function. A meta-analysis of seven rivastigmine trials (n=3,311) showed a statistically significant difference in ADAS-cog scores, in which the upper 95% CI estimate is clinically significant (weighted mean difference [WMD], -3.06 [95% CI, -4.48 to -1.65]; I^2=92.6%). The statistical heterogeneity of the analyses, however, was very high, reflecting the clinical heterogeneity in populations, medication doses, and study characteristics across trials. Only four trials (n=1,960) were conducted in persons with MCI.[208-211] These trials, for donepezil and galantamine, generally showed a small statistically significant benefit of unclear clinical importance on global cognitive function. While measures of global functioning were less commonly reported, they were still reported in the majority of trials (k=34). AChEIs appear to consistently improve measures of global functioning in people with AD in the short-term. One trial conducted in people with MCI showed a benefit for galantamine on global function, as measured by the CIBIC.[209] Outcome measures of global physical function were only reported in half the trials and showed mixed results. Therefore, it is unclear if AChEIs can improve physical functioning given the inconsistent and sparsely reported findings. Only six included trials, and seven OLE studies of included trials, examined outcomes beyond 6 months. These studies generally found persistent statistically significant benefits of unknown clinical importance for commonly reported outcomes consistent with 6-month trial outcomes. Two trials evaluating donepezil in people with MCI did not show any differences in conversion to AD at about 3 years.

Overall, side effects from these medications were quite common. Withdrawal or discontinuation was more common with AChEIs than placebo (14% for donepezil and rivastigmine, 17% for galantamine). There does not appear to be a difference in total serious adverse events for these medications across trials with limited duration of followup. Estimates of total serious adverse events, however, may be higher in observational studies than in randomized trials. The definitions of serious adverse events, which likely vary, were rarely described in the included studies. Observational studies suggest that bradycardia and adverse events related to bradycardia (e.g., fall, syncope) are increased due to AChEIs. Tacrine had very high discontinuation rates when compared with other medications in its class. While there was no mention of serious adverse events in the trials evaluating tacrine, it is known that tacrine has an uncommon but serious adverse effect of liver toxicity. Tacrine is no longer used in the United States because of these effects.

The FDA has currently only approved memantine for use in treatment of moderate to severe AD. Our review, on the other hand, was limited to those trials specifically in people with mild to moderate dementia or MCI. Based on 10 fair- to good-quality trials (n=3,015), memantine has a similar benefit as AChEIs on global cognitive functioning in people with moderate dementia, which is approximately 1- to 2-points change on the ADAS-cog at 6 months. Again, this average effect may not be clinically meaningful using commonly accepted values to interpret the clinical importance of these changes. Only one trial had longer-term followup and showed no differences in cognitive functioning between the memantine and placebo groups at 52 weeks. The impact of memantine on global functioning, as measured by the CIBIC, or global physical functioning are inconsistent. Currently, only one trial was conducted in people with MCI. Unfortunately, this trial did not report outcome measures of global cognitive or physical function. From trial data, memantine appears to be better tolerated than AChEIs, with no difference in percentages of withdrawal of medication due to adverse effects or serious adverse effects compared with placebo.

Twenty-six fair- to good-quality trials (n=5,325) evaluated other medications or supplements, including low-dose aspirin, HMG-CoA reductase inhibitors (simvastatin and atorvastatin), NSAIDs (ibuprofen, naproxen, indomethacin, and celecoxib), gonadal steroids (estrogen plus or minus progesterone and testosterone), and dietary supplements (multivitamins, B vitamins, vitamin E plus or minus vitamin C, and omega-3 fatty acids). We did not find that any of these medications or supplements had any benefit on global cognitive or physical function in people with mild to moderate dementia or MCI.

We identified 59 fair- to good-quality trials evaluating the effect of multiple different types of interventions primarily aimed at the caregiver or the patient-caregiver dyad. Among these trials, 52 trials (n=8,932) evaluated complex caregiver interventions that included a psychoeducational component. Although there were substantial clinical differences among the interventions evaluated and significant statistical heterogeneity among these trials, as a whole there was a generally consistent finding of small benefit on caregiver burden and depression outcomes in people caring for patients with moderate dementia. Pooled analyses of 24 trials (n=2,679) showed a small but statistically significant effect (SMD, -0.23 [95% CI, -0.35 to -0.12]; I^2=52.7%) on caregiver burden. Most studies reported between 0- and 5-point group differences on the 88-item Zarit Caregiver Burden Interview (CBI) or about 1- to 3-point differences on the

96-point Revised Memory and Behavioral Problems Checklist (RMBPC) caregiver bother subscale. Likewise, pooled analyses of 30 trials (n=3,537) showed a small but statistically significant effect (SMD, -0.21 [95% CI, -0.30 to -0.13]; I^2=34.1%) on caregiver depression. Most trials reported an approximate 2- to 5-point difference between groups on the 60-point Center for Epidemiologic Studies Depression Scale (CES-D). The clinical meaning of these changes in both caregiver burden and depression is unknown, but on average is likely small at best. However, effect estimates were frequently fairly wide, suggesting that there may be some subpopulations that experience clinically important benefits. The trials that were not included in pooled analyses due to missing data generally showed results consistent with meta-analyses. Our ability to interpret the clinical importance and consistency of findings for other self-reported caregiver outcomes (e.g., global stress or distress, anxiety, HRQL, self-reported health status) and institutionalization was limited by sparse reporting of these outcomes. None of the included trials reported harms. We did not identify any additional studies that explicitly evaluated harms of caregiver interventions.

Although findings were somewhat inconsistent across 15 cognitive intervention trials (n=1,128), cognitive stimulation plus or minus cognitive training (k=6; n=513) appears to improve global cognitive function in the short-term for both people with MCI or dementia. However, the limited number of trials, clinical and statistical heterogeneity combined, and very wide CIs (ranging from clinically not meaningful to a large effect) limit our ability to determine the magnitude and certainty of this benefit. Other important outcomes (e.g., physical function, HRQL, symptoms) were sparsely reported. None of the included trials reported harms. We did not identify any additional studies that explicitly evaluated harms of cognitive interventions.

Based on 10 mostly fair-quality trials (n=1,033), exercise interventions did not have a consistent benefit on global cognitive outcomes and had no benefit on patient depression outcomes. Other self-reported outcomes (e.g., physical function, HRQL) and institutionalization were not commonly reported. Two trials of a multicomponent, self-guided exercise intervention (n=220) in people with MCI found a very small benefit on global cognitive function (approximately 1 point on the MMSE or ADAS-cog) at 12 to 18 months,[212,213] but the clinical importance of this small change may not be meaningful. Although there is evidence of a benefit in a few of the better-conducted trials, we were unable to determine if there is a clinically important benefit for exercise interventions on reported outcomes due to the limited number of trials and clinical heterogeneity of the populations, exercise interventions, and reported outcomes. We found no evidence of increased total or serious adverse effects due to exercise interventions in trial participants.

Five trials (n=1,766) evaluating very different multidisciplinary care interventions found no benefit in cognitive or physical function, HRQL, or institutionalization.

Key Question 4. Do Pharmacological or Nonpharmacologic Interventions for Early Dementia or MCI in Older Adults Improve Decisionmaking, Patient, Family/Caregiver, or Societal Outcomes?

Key Question 5. What Are the Harms of Pharmacological or Nonpharmacologic Interventions for Cognitive Impairment?

Pharmacological Interventions

AChEIs (Table 11, Figures 8 and 9)

We identified one good-quality comprehensive systematic review[110] published in 2008 and 14 unique fair- to good-quality RCTs published after this review that evaluated AChEIs (k=10; n=19,384)[110,208,214-221] and memantine (k=6; n=3,462)[110,222-226] for the treatment of MCI or dementia. The systematic review included 55 trials that compared an AChEI with placebo, 50 of which are included in our review. We excluded five studies that did not meet our inclusion criteria: two because they were conducted in people with severe AD,[227,228] two because they were conducted in people with PDD,[229,230] and one because it was conducted in people with Down syndrome.[231] In total, we included 64 trials: 24 of donepezil, 12 of galantamine, 12 of rivastigmine, six of tacrine, and 10 of memantine. While most trials were conducted in people with mild to moderate AD, six trials were conducted in people with VaD, five in people with MCI, two in people with DLB, and one in people with AD and "primary degenerative dementia."

The systematic review found that using AChEIs and memantine to treat dementia can result in statistically significant but clinically marginal differences in cognition and global functioning.[110] Likewise, the trials published since the systematic review generally found similar results of statistically significant, but not necessarily clinically meaningful, differences in cognitive function between treatment and placebo groups. We found no evidence for publication bias or small study effects. Similarly, these trials generated mixed results for global and physical function outcomes. These studies were limited by their relatively short duration of followup, relatively sparse reporting of outcomes other than cognitive outcomes (including limited evaluation of global outcome measures and physical functioning), risk of bias (e.g., industry funding, unreported details of randomization, poor reporting of followup and possible attrition bias, and inadequate handling of missing data), and inclusion of mostly white populations. A brief summary of study characteristics and reported outcomes is shown in **Table 11**. More detailed study characteristics and outcomes can be found in **Appendix E Tables 1** and **2** and **Appendix F Tables 1–3**.

Donepezil

We found one good-quality comprehensive systematic review that included 21 trials meeting our inclusion criteria (n=6,506)[110] and three fair-quality trials published since the previous review (n=1,046)[208,214,215] that evaluated donepezil versus placebo. Most of the studies we identified addressed AD, but three trials included participants with MCI (n=1,881),[208,210,211] two trials included participants with VaD (n=1,219),[232,233] and one trial included participants with DLB (n=140).[214] Mean baseline MMSE scores for participants in these trials ranged from 11.8 to 27.5. The daily dosage of donepezil ranged from 1 to 10 mg, with most studies evaluating daily doses of 10 mg. These trials followed participants for 3 to 36 months. The mean age of participants ranged from 67 to 86 years. Thirty-five to 82 percent of participants were female, while 87 to 99 percent of participants were white.

All trials included in this systematic review[110] (k=21; n=6,506) and three trials published since this review[208,214,215] (n=1,047) reported measures of cognitive function. The majority of these used the ADAS-cog or the MMSE to measure cognitive function. Overall, differences in cognitive function with donepezil were statistically significant in participants with AD or VaD.[110,208] Differences from placebo in ADAS-cog scores ranged from 0.87 to 2.8 points over 3 to 36 months, less than the generally accepted clinically important change threshold of 4 points, with the vast majority of studies following patients for less than 6 months.[211,230,232-247] Only six studies included followup periods longer than 6 months,[208,210,215,223,248,249] and most of these had study periods of between 11 and 12 months.[208,223,248,249] Trials in people with MCI (k=3; n=1,881) found small statistically significant differences in cognitive outcomes for those taking donepezil that fell below clinically meaningful thresholds.[208,210,211] **Figure 8** shows summary estimates of the effect sizes for the ADAS-cog for participants with AD, MCI, and VaD. The meta-analysis of the 12 trials (n=4,636) that could be pooled showed a consistent and statistically significant difference in cognitive scores favoring donepezil (WMD, -2.03 [95% CI, -2.68 to -1.38]; I^2=67.6%) (**Figure 8**). The 15 trials (n=4,285) that reported MMSE outcomes that could be pooled also showed statistically significant, but not clinically meaningful, differences in change from baseline (WMD, 1.03 [95% CI, 0.70 to 1.36]; I^2=62.8%) (**Figure 9**). Statistical heterogeneity for both analyses was high, which likely reflects the clinical heterogeneity in age, length of followup, dementia diagnoses, and baseline MMSE scores between trials. Due to the limited reporting in the systematic review, we were unable to determine if results were similar from trials that could not be pooled.[235,238,239,246,248] In general, we found no evidence for publication bias or bias of small study effects.

Trials reported global function less frequently than cognitive function. Only 13 of 21 studies in the previous systematic review[210,211,232-234,236,240-245,249] and two of the three trials subsequent to the previous systematic review[208,214] reported global function outcomes. However, trials used different instruments to measure global functioning. Based on the results of trials that used similar measures of global functioning, there were significant differences in global function using the CIBIC-plus favoring donepezil in those with AD (k=4; n=2,049; WMD, -0.5 [95% CI, -0.5 to -0.4]), and using the Clinical Dementia Rating Sum of Boxes (CDR-SB) in those with VaD or MCI (k=2; n=1,219; WMD, -0.39 [95% CI, -0.64 to -0.15]).

Physical function outcomes were reported only in 11 of the 21 studies of donepezil included in the previous systematic review[232-234,236,241,245,248-252] and in none of the studies published since the systematic review. These trials largely used ADLs to measure physical function. Only two studies in the systematic review used the same outcome to allow for computation of a summary estimate.[232,233] These two studies demonstrated borderline statistical significance (p=0.053) for VaD favoring donepezil. The clinical impact of donepezil on physical functioning is unclear given borderline statistical significance and sparse reporting of this outcome.

Galantamine

There was one good-quality comprehensive systematic review that included 10 trials[110] (n=3,997) and two additional fair-quality trials[216,217] (n=916) that evaluated galantamine (**Table 11**). Participants in eight of these 12 trials had AD, in two trials had VaD and AD, in one trial had VaD, and in one trial had MCI. Most studies aimed for a treatment dose of 24 mg per day.

Participants were followed for a much shorter duration than in many of the donepezil trials (only 1 to 6 months). Mean MMSE scores ranged from 17.8 to 20.5, and the average age of participants ranged from 71 to 77 years. Zero to 64 percent of the participants were women, and 92 to 100 percent of participants were white.

All 12 studies reported on cognitive outcomes. Ten of these studies showed a statistically significant difference in scores favoring galantamine, but similar to donepezil, these differences are of unclear clinical importance, as changes in ADAS-cog scores ranged from 1.4 to 2.5 points. Two remaining trials had inconsistent findings. One trial in patients with AD[253] reported mixed effects, with improvement in the ADAS-cog in patients taking 24 mg per day but not 32 mg per day. Another trial of 3-day and 7-day washout periods when switching from donepezil to galantamine in patients with AD found no difference between groups.[254] A meta-analysis of nine trials (n=5,553) showed a consistent and statistically significant difference in ADAS-cog scores favoring galantamine (WMD, -2.25 [95% CI, -2.94 to -1.55]; I^2=68.4%) (**Figure 8**). Statistical heterogeneity was very high, likely reflecting differences in dementia diagnoses, medication doses, and duration of followup. We found no evidence for publication bias or bias due to small study effects.

Six trials included in the previous systematic review[252,255-259] and one subsequent trial[217] reported global function outcomes using the CIBIC-plus (n=4,346). These trials consistently showed that galantamine was associated with statistically significant better global function outcomes compared with placebo, including its use in participants with AD, VaD, and MCI. The pooled effect in the four trials from the previous review[252,255,257,259] showed a statistically significant benefit favoring galantamine using the CIBIC-plus (relative risk, 1.22 [95% CI, 1.1 to 1.3]). The remaining two trials that could not be pooled also found a statistically significant benefit for galantamine using the CIBIC-plus. One trial found that 21 percent of patients taking galantamine, compared with 37 percent taking placebo, had deterioration in global functioning at 3 months ($p<0.001$),[258] and the other trial found a standardized response mean in CIBIC-plus scores at 4 months of -0.36 between groups favoring galantamine (p=0.03).[217]

Physical function outcomes were reported for galantamine in six studies (n=3,906) using the Disability Assessment for Dementia (DAD)[217,252,258,259] and the Alzheimer's Disease Cooperative Study subscale for ADLs (ADCS-ADL).[216,255,259] Pooled estimates for studies from the systematic review found better ADL functioning in people with AD, VaD, or MCI taking galantamine than in those taking placebo (WMD for DAD, 4.2 [95% CI, 2.2 to 6.2]; I^2 not reported;[252,258,259] WMD for ADCS-ADL, 1.84 [95% CI, 0.7 to 3.0]; I^2 not reported).[255,259] The two trials of galantamine that were published after the systematic review[216,258] found no difference in physical function outcomes between groups. It is unclear if galantamine has clinically important benefit on physical functioning given the inconsistent reporting and findings of physical function outcomes.

Rivastigmine

We included eight trials (n=2,206) from a good-quality comprehensive systematic review[110] and four fair-quality trials published since the systematic review (n=2,623),[218-221] for a total of 12 trials comparing rivastigmine with placebo (n=4,829) (**Table 11**). Nine trials involved patients

with AD (n=3,476), two involved patients with VaD (n=750), and one included patients with DLB (n=120). Mean baseline MMSE scores ranged from 11.4 to 20.4, and mean ages ranged from 69 to 84 years. Women comprised 38 to 80 percent of the sample, while 0 to 95 percent of participants were white. Participants took a mean dose of rivastigmine ranging from 1 to 17.4 mg per day, with a wide range of doses represented. These studies followed participants for 3 to 12 months on average, a followup period that was longer than that for galantamine, but shorter than that for donepezil.

Eleven studies reported cognitive outcomes (n=4,802). All seven studies that used the ADAS-cog[218,219,221,260-263] found a statistically significant difference in cognitive function between groups. This difference favored rivastigmine, but did not meet the clinically meaningful threshold of a 4-point mean change, which is similar to results for donepezil and galantamine. The meta-analysis of the seven trials that could be pooled (n=3,311) showed a fairly consistent and statistically significant difference in ADAS-cog scores. The upper 95% CI estimate was also clinically significant (WMD, -3.06 [95% CI, -4.48 to -1.65]; I^2=92.6%) (**Figure 8**). The pooled effect among seven trials (n=2,854) reporting MMSE scores at followup was not statistically significant (WMD, 0.61 [95% CI, -0.10 to 1.32]; I^2=90.9%) (**Figure 9**). Statistical heterogeneity was again very high, which reflects the clinical heterogeneity in dementia diagnoses, mean MMSE scores, mean doses, age, sex, race, and length of followup.

Nine of the 12 included trials reported global function. Five trials (n=3,624) included in the systematic review (WMD, -0.36 [95% CI, -0.45 to 0.27])[260-264] and the one subsequent trial[219] (n=678) that used the CIBIC-plus to rate global function (mean difference in CIBIC-plus scores, -0.4; p<0.05) found statistically significant differences that favored rivastigmine. For the two trials (n=710) that used the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) to rate global functioning, one trial of patients with VaD found no statistically significant difference between groups.[218] In contrast, a trial of patients with AD found a statistically significant benefit in people randomized to a 9.5 mg per 24 hour rivastigmine patch (mean difference, -0.3; p=0.01) and 12 mg per day rivastigmine capsules (mean difference, -0.3; p=0.009), but not for those patients in a higher dose arm (17.4 mg/24 hour patch).[221]

Only three rivastigmine trials (n=1,468) included in the systematic review[260,262,263] assessed physical function and did not find a statistically significant positive impact with rivastigmine on this outcome. These trials assessed outcomes in patients with AD via the Progressive Deterioration Scale. All four trials published subsequent to the systematic review assessed physical outcomes (n=2,623).[218-221] Studies that included patients with AD found significant differences in physical outcomes at 6 months (n=1,873),[219,221] while those that enrolled patients with VaD did not find a statistically significant difference (n=750).[218,220] It is unclear if rivastigmine has clinically important benefits on physical functioning given the sparse reporting of these outcomes and inconsistent findings.

Tacrine

Tacrine is an older AChEI that is no longer used in the United States. Only six trials (n=994)[265-270] comparing tacrine with placebo were published between 1991 and 2002. These trials were all

included in the previous systematic review. Participants in these trials had AD and mean MMSE scores ranging from 16.2 to 18.5, with daily dosages of tacrine from 80 to 150 mg. Followup ranged from 3 to 9 months. Many of the tacrine trials did not report location or race/ethnicity.

None of the tacrine studies showed clinically meaningful improvement in cognitive function outcomes. The meta-analysis of the two trials (n=763) that could be pooled showed nonstatistically significant differences in MMSE scores between groups (WMD, 0.86 [95% CI, -0.05 to 1.77]; I^2=0.0) (**Figure 9**). Two (n=817)[265,270] of the three trials that evaluated global function (n=917)[265,269,270] found statistically significant improvement in this domain. None of the studies evaluated physical function outcomes, as reported by the systematic review.

Memantine

One good-quality systematic review[110] of five trials (n=1,959)[271-275] and five subsequent trials of fair- to good-quality[224-226] (n=1,506) evaluated memantine versus placebo (**Table 11**). Participants in these trials were diagnosed with AD (k=7; n=2,505), VaD (k=2; n=900), or MCI (k=1; n=60), and mean baseline MMSE scores ranged from 7.9 to 28.8. Memantine doses ranged from 5 to 20 mg per day, with most studies evaluating 20 mg per day. These studies followed participants for a relatively short period of time (3 to 12 months). The mean age of participants ranged from 67 to 78 years. About half of the participants were women and almost all of the participants were white.

Of the six studies of memantine in patients with AD, four reported no difference in cognitive outcomes (n=1,433),[223,224,226,273] while the remaining two reported differences in favor of memantine that were statistically significant but likely not clinically meaningful (n=807).[272,274] The two trials conducted in patients with VaD[271,275] (n=900) found differences between groups on the ADAS-cog that were statistically, but likely not clinically, significant (WMD, -2.21 [95% CI, -3.3 to -1.2]; I^2=31.5%). The study involving participants with MCI did not report cognitive outcomes.[225] A meta-analysis of five trials (n=2,124) showed a consistent and statistically significant difference in ADAS-cog scores favoring memantine that did not reach clinical importance (WMD, -1.36 [95% CI, -2.02 to -0.70]; I^2=31.5%). Pooled results for the MMSE in the five trials (n=1,863) that could be pooled similarly showed a small but statistically significant effect (WMD, 0.45 [95% CI, 0.023 to 0.89]; I^2=36.7%) (**Figure 9**) that is likely not clinically meaningful. Statistical heterogeneity in these trials was lower than that observed in similar analyses for AChEIs, which likely reflects the smaller variation in patient populations and treatments between trials.

The three trials in the previous review that evaluated memantine in patients with AD (n=1,050)[272-274] found a significant difference in global outcomes as measured by the CIBIC-plus between memantine and placebo groups (WMD, -0.3 [95% CI, -0.4 to -0.1]; I^2=0%). However, global outcomes were not significantly different between groups at 6 months in the two trials[224,226] (n=830) that included participants with AD that were published after this review. Two trials in people with VaD (n=900) from the previous review found no benefit of memantine on global function outcomes. One trial in patients with MCI (n=60) published since the previous review did not report this outcome.

Results were mixed for the five trials[224,226,272-274] (n=1,962) that reported on physical function outcomes. All five of these studies used the ADCS-ADL to measure physical function. Three trials conducted in people with AD (n=1,059)[272-274] found that participants who received memantine had better physical function outcomes than those taking placebo (WMD, 1.4 [95% CI, 0.4 to 2.4]; I^2=5.1%). However, two other trials conducted in people with AD found no statistically significant difference in physical function between groups (n=903).[224,226] Two trials conducted in patients with VaD also found no difference in physical function outcomes (n=900).[271,275] The trial of patients with MCI did not report this outcome.[225]

Evidence of Longer-Term Effects

The vast majority of AChEI and memantine trials lasted 6 months or less. Only seven RCTs[210,248,249,208,223,262,276] and eight OLE studies[277-285] examined outcomes longer than 28 weeks.

Donepezil. There were five RCTs[208] and four OLEs[277-279] that examined longer-term outcomes in donepezil. For cognitive outcomes, one RCT[249] and one OLE noted statistically significant differences in patients with AD at 52 weeks (n=286)[249] and 54 weeks (30 weeks after the 24-week trial) (n=885);[279] however, the differences were not large enough to conclude that they were clinically meaningful. Another OLE of patients with AD showed no differences in cognitive outcomes at 132 weeks (n=579).[278] In participants with MCI, differences in cognitive outcomes were statistically significant in favor of donepezil but not thought to be clinically meaningful in a 48-week RCT (n=821)[208] and a 76-week (28 weeks after the 48-week trial) OLE (n=145).[277] Two RCTs examined conversion from MCI to AD in patients randomized to donepezil, vitamin E, or placebo: one RCT of 769 patients with amnestic MCI found decreased conversion to AD in the donepezil group in the first 12 months but no difference at 3 years,[210] while the other RCT of 756 patients found donepezil delayed conversion to AD at 1.7 and 2.2 years but not at 2.7 years, and not in patients without depression.[276] Participants with AD treated with donepezil had better global function at 52 weeks in an RCT of 286 patients.[249] Results were not statistically significant in participants with AD in a 54-week OLE (n=885)[279] or in those with MCI in a 48-week RCT (n=821)[208] or a 76-week OLE (n=145).[277] Regarding physical function in patients with AD, one RCT found donepezil delayed clinically evident functional decline by 5 months at 54 weeks (n=431),[248] another RCT found donepezil delayed decline in ADLs at 52 weeks,[249] and a third RCT found donepezil led to less caregiver time at 52 weeks (but not at earlier timepoints).[285]

Galantamine. There were three OLEs of 6-month trials of galantamine ranging from 52 to 130 weeks, with sample sizes ranging from 326 to 459.[282-284] All found differences in cognitive outcomes in participants with AD and VaD that were statistically significant but likely not clinically meaningful. One OLE found significant differences in physical functioning at 52 weeks in favor of galantamine (n=459).[282]

Rivastigmine. There was one OLE of an included rivastigmine study beyond 25 weeks; however, no cognitive outcomes were reported.[280] There was only one longer-term study of rivastigmine, a 52-week RCT of 44 participants with AD, which showed statistically significant differences in cognitive outcomes in which the upper CIs reached levels of clinical importance (ADAS-cog score with rivastigmine, 0.8+0.7; ADAS-cog score with placebo, -4.5+0.8; $p<0.001$).[262]

Differences in global and physical functioning were statistically significant in favor of rivastigmine at 52 weeks.[262]

Memantine. There were two longer-term studies of memantine: one RCT of 278 patients with AD that did not show any differences in cognitive function at 52 weeks,[223] and one 52-week OLE that did not report on cognitive, global, or physical function outcomes.[281]

Adverse Effects of AChEIs and Memantine (Table 12, Figures 10 and 11)

The good-quality systematic review conducted by Raina and colleagues included harms reported in medication trials and their OLE studies.[110] We included trials and their associated OLE studies published after those included in the systematic review, as well as several observational studies that focus solely on harms of these medications. We included 50 trials from the systematic review and 16 trials, including two open-label trials, were identified since this systematic review. Harms were reported in 57 of these 66 trials. We also included six studies that were OLEs (published since the systematic review) of included trials that also reported harms. There were an additional 13 observational studies that also addressed harms.

In general, most trials were conducted in North America or western Europe. Participants in these trials had mean ages ranging from 54 to 86 years and had a good representation of both men and women (**Table 12**). The mean baseline MMSE score ranged from 11 to 28. With the exception of trials conducted in people with MCI, the average MMSE score was generally consistent with participants having moderate (as opposed to mild) dementia. Duration of followup in trials was generally short, usually less than 12 months, although it ranged from 3 to 36 months. The populations in observational studies were also from North America or western Europe, with mean ages ranging from 73 to 83 years. In general, baseline MMSE scores, along with other baseline patient characteristics, were not reported. Observational studies generally included any patient receiving the medication (e.g., as noted through a pharmacovigilance database or health system, such as the VA). The majority of these patients likely had mild to moderate dementia, except for those taking memantine. Doses of medications used in trials in observational studies were representative of dosing used in actual practice.

Most studies reported a combination of adverse outcomes that included withdrawals from trial or discontinuation of medication due to harms/tolerability, serious or severe harms, and specific types of harms/side effects (e.g., nausea, weakness/malaise, bradycardia). We focus on total adverse events (when reported), withdrawal/discontinuation due to adverse events, and serious adverse events. The Discussion section details the types of adverse events and side effects from medications.

Overall, side effects or harms are quite common with these drugs. Withdrawal or discontinuation is more common with AChEIs than placebo (**Figure 10**). Discontinuation ranged from 14 percent (donepezil and rivastigmine) to 44 percent (tacrine). Memantine appears to be better tolerated, with no difference in percentages of withdrawal of medication compared with placebo (**Figure 10**). Across trials, there does not appear to be a difference in total serious adverse events for donepezil, galantamine, rivastigmine, or memantine (**Figure 11**). One large observation study had higher estimates of serious adverse events compared with estimates from trials. Definitions

for serious adverse events varied across studies and were often not specified. Followup for most trials was generally 1 year or less. Nearly all trials were industry funded. Case-control studies suggest that bradycardia is increased due to AChEIs, as are adverse events related to bradycardia (e.g., fall, syncope).

Donepezil. The good-quality systematic review included 21 trials of donepezil (n=6,506) conducted in patients with mild to moderate dementia (k=19) or MCI (k=2).[110] The systematic review did not report proportion of total adverse events in the trials. Seventeen of the 21 trials included in the review reported withdrawal due to adverse effects. Four of the five new fair-quality trials (n=2,109) also reported withdrawal due to adverse effects.[208,214,286,287] Three of these trials, however, had only 3 months of followup.[214,286,287] Overall, there was an increased risk for withdrawal due to medication adverse events (RR, 1.82 [95% CI, 1.52 to 2.18]) (**Figure 10**). In the intervention arm, 14.5 percent had adverse events resulting in discontinuation of the medication versus 7.7 percent in the placebo group. Serious adverse events were less commonly reported (15 of 25 trials). We did not identify a difference in serious adverse events (10.8% in drug group and 10.4% in placebo group) (**Figure 11**).

We also included five fair- to good-quality observational studies to evaluate harms of donepezil (n=90,267). Two of these studies reported the relative frequency of adverse effects using medication surveillance systems of voluntary reporting of adverse effects. These studies found that gastrointestinal symptoms (i.e., nausea/vomiting, diarrhea) were the most common adverse events and that bradycardia, weakness, and convulsions were the most common serious adverse events.[288,289] Two well-conducted case-control studies found that bradycardia and bradycardia-related hospital admissions were more common in people taking donepezil.[290,291]

Galantamine. We included one good-quality systematic review of 10 trials of galantamine (n=5,090) conducted in patients with mild to moderate dementia (k=9) or MCI (k=1).[110] We also included two additional trials (n=918) that were published after the review. Ten of these 12 trials reported withdrawal due to medication of about 17 versus 7 percent in the placebo group (RR, 2.50 [95% CI, 1.78 to 3.50]) (**Figure 10**). Eight of the 10 trials reported serious adverse events. These trials identified no significant difference in proportions of serious adverse events (11% in the drug groups and 10% in the placebo groups) (**Figure 11**). Only one observational study (n=324) specifically addressed harms of galantamine.[290] This good-quality case-control study found no statistically significant increase in risk of bradycardia in those taking galantamine.

Rivastigmine. We included one good-quality systematic review of eight trials of rivastigmine (n=2,206) in patients with mild to moderate dementia.[110] We also included four trials (n=2,623) that were published after this systemic review. Ten of these 12 trials reported withdrawal due to medication. These withdrawal rates were about 14 percent in the intervention group versus 6 percent in the placebo group (RR, 2.35 [95% CI, 1.71 to 3.21]) (**Figure 10**). Serious adverse events were less commonly reported (six of 12 trials), and we found no significant difference in proportions of serious adverse events between study arms (13% in the drug groups and 12% in the placebo groups) (**Figure 11**). Only one observational study (n=324)[290] specifically addressed harms of rivastigmine. This good-quality study found an increase in risk of bradycardia in those taking rivastigmine.

Tacrine. We included only one good-quality systematic review of six trials of tacrine (n=994) from the 1990s.[110] Four of the six trials included in this review reported withdrawal due to medication (44% in the tacrine groups vs. 11% in the placebo groups). None of these trials reported on serious adverse events. Tacrine has an uncommon but serious side effect of liver toxicity, and as a result is no longer used in the United States.

Memantine. We included one good-quality systematic review of five trials of memantine (n=1,959) in patients with mild to moderate dementia.[110] We also included five fair- to good-quality trials (n=1,506) published after the systematic review. One of these trials was conducted in people with MCI.[225] Nine of the 10 trials reported withdrawal due to the medication, while another eight trials reported serious adverse events. Overall, we found no significant differences in proportions of withdrawal (about 9% in each group) or serious adverse events (about 12% in each group) (**Figures 10** and **11**). All of these trials, however, had less than 1 year of followup. One study reported safety data from two open-label multicenter studies (n=4,305), which showed similar rates of adverse events as trials and that adverse events were more common with increasing age, and that people with less severe disease were more likely to discontinue treatment.[292] Two fair-quality observational studies (n=5,378) showed that the discontinuation rate of memantine (up to 20 months) was about 40 percent. Bradycardia, weakness, and convulsions were the most commonly reported adverse events.[288,293]

Any AChEI and/or Memantine. We also included eight fair- to good-quality observational studies that examined the harms of any medication (i.e., did not separate harms by specific drug). From these studies, it appears that the proportions of people with serious adverse effects may be higher than that observed in trials, at about 18 percent.[294,295] Central nervous system disorders were the most commonly serious adverse events, followed by heart rate/rhythm disorders and gastrointestinal disorders.[296] In people with chronic obstructive pulmonary disease and dementia, there was no increased risk of adverse pulmonary events in those receiving AChEIs versus nonusers.[297] Well-conducted case-control studies show that people taking AChEIs are at increased risk for bradycardia and bradycardia-related events such as falls, syncope, and pacemaker insertion.[290,298] One large comparative study (n=46,737 Medicare beneficiaries) showed that the cardiovascular safety profiles of AChEIs and memantine did not differ substantially in the Medicare population.[299]

Other Medications (Table 13, Figure 12)

We identified 26 trials (n=5,325) that evaluated 1) medications primarily aimed at cardiovascular risk reduction to treat VaD, including antiplatelet medications (k=2; n=459) and HMG-CoA reductase inhibitors (k=4; n=1,153); 2) NSAIDs (k=4; n=959); 3) gonadal steroids (estrogen plus or minus progesterone [k=4; n=277] and testosterone [k=1; n=18]); and 4) dietary supplements (i.e., multivitamins [k=1; n=89], B vitamins [k=7; n=1294], vitamin E plus or minus vitamin C [k=3; n=522], and omega-3 fatty acids [k=4; n=1,145]) (**Table 13**). We did not include trials evaluating herbal supplements. Twenty-one of 26 trials were conducted exclusively in people with mild to moderate dementia. One trial that evaluated aspirin and supplements in a factorial design was conducted in a mixed population (one third of which had MCI),[300] and four supplement trials were conducted exclusively in people with MCI.[301-304] All but one[302] of the included trials reported global outcome measures of cognitive function. While most of these

trials also included some outcome measure of physical function or neuropsychiatric disturbances (including depression), other outcomes of HRQL and caregiver burden were not consistently reported. In general, trials did not find a benefit in reported outcomes across the different interventions in different populations. Limitations in the primary evidence do not allow for any meaningful analyses of outcome findings by important subgroups, such as by age, sex, race/ethnicity, type of dementia, or level of cognitive impairment. **Table 13** provides a brief summary of study characteristics and reported outcomes and **Appendix F Table 4** provides more detailed study characteristics and outcomes.

Aspirin and HMG-CoA Reductase Inhibitors

Six fair-quality trials evaluated low-dose aspirin (acetylsalicylic acid [ASA] 75 or 81 mg) or HMG-CoA reductase inhibitors (simvastatin 40 or 80 mg, atorvastatin 80 mg). We found no trials evaluating other medications aimed at cardiovascular risk reduction (e.g., antihypertension medications) that met our inclusion criteria. Although these medications are primarily aimed at mitigating vascular risk, the trials were conducted in people with AD (although some patients had comorbid VaD). The average age of patients in the trials ranged from 68 to 79 years. The trials included both men and women and were conducted in primarily white populations in the United States, United Kingdom, and Germany. All the trials were conducted in people with known dementia (mean baseline MMSE score, 17.5 to 21.9), except for one ASA trial that included a mix of patients (about one third MCI and two thirds dementia).

While the trials of ASA and HMG-CoA reductase inhibitors were generally well conducted, each had at least one major limitation. These limitations included small sample size, limited duration of followup (<12 months), attrition (>20%) or differential attrition, and unclear blinding of outcomes. Additionally, HMG-CoA reductase inhibitor trials were exclusively or partially industry funded.

The two fair-quality low-dose ASA trials (n=459) showed no difference in global cognitive or physical function outcomes between the ASA and placebo groups at 3 months[300] or 36 months.[305] The larger trial (n=310) with longer followup (36 months) also found no difference in measures of neuropsychiatric symptoms and caregiver burden.[305] This was the only trial that reported harms of ASA and found an overall increased number of people with any adverse events with ASA versus placebo control (53% vs. 37%, respectively). This trial also found an increased number of serious bleeding events (6% vs. 1%, respectively).

The four fair-quality HMG-CoA reductase inhibitor trials (n=1,153) showed no difference in global cognitive function at 6 to 18 months.[306-309] We also quantitatively pooled cognitive function outcomes among the three trials (n=1,064) that reported sufficient data to determine if the individual trials' null results were simply because they lacked power to detect a finding.[306-308] This pooled analysis of standardized effect sizes of ADAS-cog scores resulted in clearly null findings (Hedge g, -0.08 [95% CI, -0.98 to 0.82]; I^2=0%) (**Figure 12**). Three of these four trials (n=1,109) also showed no difference in physical function or neuropsychiatric symptoms.[306,307,309] One trial (n=63) found a small improvement in depression (Geriatric Depression Scale [GDS]) in those receiving atorvastatin versus placebo at 12 months. Despite this result, there was no difference in overall neuropsychiatric symptoms (neuropsychiatric inventory [NPI]). Three of the

four trials (n=1,090) reported harms of HMG-CoA reductase inhibitors. Only one trial that evaluated a high dose of atorvastatin (80 mg) found evidence of increased adverse events in the atorvastatin versus placebo groups, with greater nonadherence due to adverse events (17.8% vs. 9.5%) and an increase in total treatment-related adverse events (32.8% vs. 18.8%). There was no statistically significant difference, however, in total adverse events or serious adverse events.

NSAIDs

Four fair-quality trials evaluated four different NSAIDs (ibuprofen 800 mg, naproxen 220 mg, indomethacin 100 mg, and celecoxib 40 mg daily) given alone or in combination with a proton pump inhibitor. These trials were all conducted in persons with mild to moderate AD, with a mean MMSE score ranging from 19.6 to 20.9. The average age of participants was 73 or 74 years and about half were women. Trials were conducted in the United States or western Europe and rarely reported the race/ethnicity of participants.

Trials were generally well conducted, but each had at least one major limitation, including small sample size, differences in baseline characteristics, and attrition (>20%) or differential attrition. The celecoxib trial was industry funded.

Four fair-quality NSAID trials (n=959) showed no difference in global cognitive or physical function outcomes at 12 to 18 months between the medication and placebo groups.[310-313] Similarly, pooled results among the three trials (n=399) with sufficient cognitive outcome data to be quantitatively combined showed null findings (**Figure 12**).[310-312] HRQL, depression, neuropsychiatric symptoms, and caregiver burden were not consistently reported and showed no differences when reported. None of the four trials had statistically significant differences in withdrawal from trials due to adverse events. Three trials (n=827) reported no statistically significant differences in adverse events between the medication and placebo group. Only the celecoxib trial (n=425) reported total adverse events and found no statistically significant differences between the treatment arms.

Gonadal Steroids

Five fair-quality trials evaluated gonadal steroids: estrogen (k=3; n=212), estrogen plus progesterone (k=1; n=65), or testosterone (k=1; n=18). Estrogen doses ranged from 0.625 to 1.25 mg daily, progesterone 0.5 mg daily, and testosterone (transdermal/topical) 75 mg daily. Trials of estrogen plus or minus progesterone were only conducted in women. Likewise, the testosterone trial was conducted in only men. The average age of patients in the trials ranged from 69.8 to 81 years. All of the trials were conducted in mostly white populations, except for one estrogen replacement trial conducted in Taiwan.[314] All the trials were conducted in people with known AD (mean baseline MMSE score, 19.5 to 22), except for one estrogen trial in Taiwan in which the mean MMSE score was much lower (16.2).

Included trials were small and had limited followup (<12 months). Other trial limitations included attrition (>20%) or differential attrition and differences in baseline characteristics.

The four fair-quality estrogen trials (n=277) all showed no difference in global cognitive

function outcomes at 3 to 12 months between the gonadal steroid and placebo groups, as did the one small testosterone trial (n=18). Pooled analysis of the standardized effect sizes of global measures of cognitive function also showed null findings (**Figure 12**). Three of the four estrogen trials (n=227) also showed no difference in physical function outcomes between treatment and control arms.[315-317] We identified no significant differences in other outcomes of HRQL and symptoms, and these outcome measures were sparsely reported. Harms outcomes were not consistently reported. Three trials reporting withdrawal due to adverse events with estrogen or progesterone found no differences between the treatment and placebo groups.[314,316,318] While one trial reporting total and serious adverse events of estrogen plus progesterone found no differences between treatment arms, one trial with estrogen alone did find an increase in total adverse events in women receiving estrogen compared with placebo, mainly due to vaginal bleeding (44% vs. 0%, respectively).

Dietary Supplements

Twelve fair- to good-quality trials evaluated dietary supplements, including one multivitamin trial (n=89); seven B vitamin (n=1,294) trials that included folic acid and vitamins B6 and B12; three vitamin E trials (n=522); and four omega-3 fatty acid trials (n=1,145) that included docosahexaenoic acid plus or minus eicosapentaenoic acid. Doses of supplements varied somewhat but were all within the range of one another (**Table 13**). One exception is one trial that evaluated omega-3 fatty acids paired with vitamin E and used substantially lower doses of vitamin E (on the order of 100 times less); therefore, this trial is considered to primarily evaluate the effects of omega-3 fatty acids.[319] All but five of these trials were conducted exclusively in people with mild to moderate dementia; one trial evaluating B vitamins (folic acid and B12) and vitamins E and C in a factorial design was conducted in a mixed population (one third of which had MCI),[300] and four supplement trials (two evaluating B vitamins and two evaluating omega-3 fatty acids) were conducted exclusively in people with MCI.[303,304] Because results of these trials do not vary by severity of cognitive impairment, we discuss the results of these trials together (as opposed to MCI vs. dementia).

The average age of patients in these 10 trials ranged from 70 to 78.2 years and they included both men and women. Trials were conducted in United States, northern Europe (United Kingdom, Sweden, the Netherlands), Australia, and Asia (Hong Kong and Japan). The mean MMSE score in trials of patients with dementia ranged from 12.3 to 23.5. The trial with the lowest mean MMSE score (12.3) was conducted in an assisted living facility, evaluating vitamin E.[320] The mean MMSE score in trials conducted in patients with MCI ranged from 27.2 to 29.0.

Included trials were generally well conducted. We included three good-quality trials with no significant threats to validity.[304,320,321] The remaining nine trials had at least one major limitation, which included suboptimal reporting of details to assess risk of bias and attrition (>20%) or evidence of attrition bias.

Collectively, these trials (k=12; n=2,608) represented a variety of different interventions in somewhat heterogeneous clinical populations. Despite this diversity, none of the trials found a difference in global cognitive outcomes between the supplement and placebo groups. Our ability to interpret these results or pool the analyses is limited due to differences in supplements and

populations and limited number of trials providing sufficient data to be included in the analysis. Despite these limitations, pooled analyses (k=6; n=1,450) also had null findings (**Figure 12**).

Eight of the 12 included trials also reported outcomes of global physical function, none of which found any differences between treatment arms. In addition, eight of the 12 included trials reported some measure of neuropsychiatric disturbances and/or depression. Only one small trial (n=54) conducted in people with MCI showed a benefit of omega-3 fatty acids on depression scores at 6 months.[302] Other outcome measures of HRQL and caregiver burden were sparsely reported and also found no significant differences between treatment arms. These trials did not consistently report harms. Among the six trials that reported total adverse effects, serious adverse effects, or discontinuation of supplement due to adverse effects, none of the trials found statistically significant differences of events between treatment arms. One trial of high-dose vitamin E (1,000 IU daily) in more cognitively impaired patients (mean MMSE score, 12.3) in assisted living reported more syncopal events in the vitamin E group versus the placebo group (7% vs. 4%, respectively).

Nonpharmacologic Interventions

Caregiver Interventions (Table 14, Figures 13 and 14)

We identified 59 trials (n=8,932) that targeted the caregiver or the caregiver-patient dyad with the primary aim of improving caregiver outcomes or skills, representing a wide variety of different interventions. Most of the trials (k=52; n=8,103) evaluated interventions with some type of psychoeducational component. These interventions provided information about dementia and/or caregiving and sought to increase caregiver skills (specific caregiving skills or general skills, such as problem solving and communication applied to caregiving). Other trials evaluated interventions that provided little or no dementia education or caregiver skills development, but instead involved peer support only[322-325] (k=4; n=644), physical activity for caregivers[326-328] (k=3; n=293), or an assessment and treatment plan development (k=1; n=50).[329] Due to the different types of interventions, we summarize findings for the 52 psychoeducation interventions first and other interventions separately. A group of trials, the Resources for Enhancing Alzheimer's Caregiver Health (REACH) trials,[325,330-333] were part of a consortium that used common methods and measurement instruments, but examined different intervention approaches. We excluded one of the REACH trials from this review because it was limited to patients with moderate to severe dementia. The remaining REACH trials were treated as independent studies. **Table 14** provides a brief summary of study characteristics and reported outcomes. **Appendix E Tables 4–8** and **Appendix F Tables 5–7** provide more detailed study characteristics and outcomes.

Psychoeducation Interventions

Intervention Characteristics. The psychoeducation intervention trials encompassed a wide range of approaches. While the target of the intervention was usually the caregiver or the caregiver-patient dyad, two trials targeted the whole family[334,335] and two trials focused on provider training.[336,337] The most common format was for interventionists to meet individually with caregivers, dyads, or families (k=32). A substantial number of interventions, however, took place

in group settings (k=17), and three trials used computer-based systems (usually linked to a phone system) to deliver education, training, and support from other caregivers.[333,338,339] Interventions took place in medical settings or in the home. In addition to providing information about dementia and available community resources, most interventions also included training in stress management, problem solving, and communication techniques. A variety of additional components were sometimes used, including supportive counseling (counseling focused on the caregiver's emotional or psychological issues), home safety assessments or information, occupational therapy, and environmental modifications.

Psychoeducation intervention providers were generally health care nurses or social workers, or health educators of some kind. Four trials that integrated occupational assessment and interventions used occupational therapists as the interventionist.[340-344] Ten trials used a medical liaison for care or case management in addition to psychoeducation.[332,336,345-351] Interventions in included trials ranged in intensity and duration; the number of sessions ranged from three to 18 sessions and the median number of sessions was 10 sessions (interquartile range [IQR], 6 to 12). The duration of included interventions ranged from 3 weeks to more than a year (median, 17 weeks [IQR, 7 to 44]).

Population Characteristics. The patients included in these trials had mild to moderate dementia and were community-dwelling individuals who required caregiving. The average MMSE score was consistent with patients having moderate, as opposed to mild, dementia. Some trials had a minimum requirement for time spent in caregiving, which ranged from one visit per week to (most commonly) 4 hours per day. All of the REACH trials[325,330,332,333,352] required 4 hours per day of caregiving, as did three others.[353-355] The average MMSE score was 15.9 across all studies reporting it (n=5,274). Baseline MMSE scores were an average of 5.3 points lower in trials conducted in the United States (mean score, 13.6 in U.S.-based trials vs. 18.9 in other trials).

Half (k=26) of the 52 psychoeducation trials were conducted in the United States. The remaining studies were conducted in Europe,[334,337,343,348,350,355-360] Australia,[335,361] Canada,[362-365] Taiwan,[347, 353,366] and Hong Kong.[351] The majority (76%) of caregivers in psychoeducation interventions were women, and about half were the patients' spouses. Trials conducted outside of the United States rarely reported race/ethnicity distribution of their samples, and samples in U.S.-based trials generally included less than one third nonwhite participants. However, at least 40 percent of the participants in four trials were black or Latino.[325,330,332,367]

Study Characteristics. We only rated four of the psychoeducation trials as good quality,[336,337,356, 368] including both trials that targeted providers. These trials used good procedures and statistical methods and had followup on at least 80 percent of their participants. The remaining 46 trials were rated fair quality for a variety of reasons. Most commonly, more than a third of the trials failed to report whether allocation was concealed, almost half of the trials failed to describe blinding of outcomes assessment, and just under one third reported followup on less than 80 percent of participants after 6 to 12 months.

Findings. Burden and depression were the two most commonly reported caregiver outcomes; 81 percent of the psychoeducation trials reported at least one of these two outcomes. None of the trials reported on adverse effects. Caregiver burden was reported in 29 (n=4,598) of the trials that

employed psychoeducation interventions, and this burden was measured by a variety of self-report instruments (**Appendix E Table 6**). The Zarit CBI was the most commonly used instrument, which defined burden as a subjective sense that resources are insufficient to meet role demands. This instrument specifically measures perceived social, physical, financial, and emotional burden of caregiving, as well as providing a total summary score.[369] This instrument has been widely used and has demonstrated acceptable reliability and construct validity, although given the multidimensional nature of caregiver burden, a single summary score is limited in the degree to which burden can be fully captured. The RMBPC caregiver bother subscale was the second most commonly used instrument. This instrument asks caregivers to rate the degree to which they are bothered by 24 patient behaviors.[370]

Effect sizes for caregiver burden were generally small, and 11 (38%) of the trials that reported this outcome found a statistically significant benefit of psychoeducation interventions after 3 to 18 months.[145,330,342,346,347,352,355,363,367,371,372] The standardized pooled effect for those reporting sufficient data to be included in the meta-analysis (k=24; n=2,679) showed a small but statistically significant effect (SMD, -0.23 [95% CI, -0.35 to -0.12]; I^2=52.7%) (**Figure 13**). Statistical heterogeneity was fairly substantial, consistent with the clinical heterogeneity among the interventions studied. Using visual inspection of forest plots, summary tables, and exploratory meta-regressions, we determined that no design feature, population characteristic, or treatment component robustly explained the variability in effect sizes (including time to followup, study quality, year of publication, type of control group used, caregiver age, percent of caregivers who were female, patient baseline MMSE score, number of sessions offered as part of the intervention, total hours of contact with an interventionist, group sessions, one-on-one sessions, peer support, problem-solving training, communication training, stress management, supportive counseling, provision of dementia information, use of active techniques, intervention geared toward whole family, home safety assessment or information, direct patient care, care or case management, or total number of specified treatment components included in the intervention). However, provision of information about dementia did have a statistically significant association with effect size (p=0.048), in that effect sizes were slightly larger for studies that clearly provided caregivers with information about dementia, such as prevalence, course, and possible treatment options. We could not include six of the studies (n=1,059) that reported burden in the meta-analysis because they were missing important information or reported an incompatible outcome.[334,347,351-353,362] In these studies, the effect sizes were similarly small, with few statistically significant group differences. Overall, we found no evidence of bias of small study effects (i.e., smaller or more imprecise trials showing larger effects).

The clinical importance of these small changes, however, is unclear. Most studies reported between 0- and 5-point group differences on the 88-item Zarit CBI or about 1- to 3-point differences on the 96-point RMBPC caregiver bother subscale. Baseline Zarit CBI scores ranged widely across studies, and only one study reported average changes of 6 points or more in either group (the equivalent of changing from being bothered "quite frequently" to "rarely" on three of 22 items). However, CIs were frequently quite wide, suggesting the possibility that some patients showed substantial benefit and others did not benefit at all. Unfortunately, we could not identify such a subgroup based on study-level data. While we did not identify a relationship between study size and effect size, the high degree of statistical and clinical heterogeneity limits confidence in any single point estimate from a meta-analysis. There is no indication that omitting

six trials with missing or incompatible data from the meta-analysis substantially biased the analysis. The true average effect is likely small at best, which is consistent with the results of the meta-analysis.

Thirty-four of the psychoeducation trials (n=5,423) reported caregiver depression, measured by a variety of self-report instruments (**Appendix E Table 7**). The CES-D, a 20-point screening instrument, was the most commonly used instrument.[373] Other instruments were only used in one or two studies. While the effect sizes were generally small, 16 (47%) of the trials reporting caregiver depression found statistically significant results after 3 to 24 months.[145,335,342,343,345,346,352, 353,359,367,368,371,374-377] Our meta-analysis included the pooled effect for 30 trials (n=3,537) and found a small but statistically significant effect (SMD, -0.21 [95% CI, -0.30 to -0.13]; I^2=34.1%) (**Figure 14**). We could not include six of the trials reporting depression in the meta-analysis due to missing or incompatible data. Three of these studies showed statistically significant benefit in reduction of symptoms or in the percent of participants meeting a threshold.[342,352,353,376,378,379] Evidence regarding small study effects bias was mixed. Begg's test and the trim-and-fill procedure did not suggest small study bias; however, Egger's test of bias was statistically significant, and a cumulative meta-analysis sorted by the study's standard error (a measure of precision and related to effect size) showed generally increasing effect sizes as studies with larger standard errors were added to the analysis. Due to this potential bias, the pooled estimate may overestimate the true effect.

Similar to changes in caregiver burden, the clinical importance of these small changes in depression scores is unclear. Most trials reported an approximate 2- to 5-point difference between groups on the 60-point CES-D. A 2-point difference could mean that a person moved from endorsing a symptom 3 to 4 days to rarely or never in the past week, or from 5 to 7 days to 1 to 2 days in the past week. In these trials, control groups typically changed very little and intervention groups showed small improvements. Baseline depression was typically in the minimal or mild range, or an average score of 12 to 15 on the CES-D (where 16 indicates possible depression). Several study features were related to effect size in exploratory qualitative and quantitative analysis, including year of publication (later years were associated with smaller effects), baseline patient MMSE score (smaller effects were seen in trials with higher baseline average MMSE scores), and the intervention's provision of dementia information (trials that did not clearly provide general information about dementia had effect sizes that were smaller than average). Trials reported a wide variety of additional self-reported outcomes that were similar to burden and depression, including adjustment to a relative's illness, global stress or distress, anxiety, HRQL, or self-reported health status. However, most of these outcomes were only reported in one to three studies and results were generally mixed. Emotional distress was the most commonly reported of these outcomes, as measured by the General Health Questionnaire. This result was reduced with psychoeducational interventions compared with control groups in four of five studies reporting this result, although other measures of global distress usually showed no group differences.

Twenty-one psychoeducation trials additionally reported institutionalization. While few of the trials were powered to detect a change in this outcome, many reported on institutionalization when describing participant attrition. Eight of the trials identified institutionalization as a primary outcome,[335,337,344,347-349,356,361] and all but one of these trials were conducted outside the

United States.[349] Group differences were only statistically significant in one older trial.[361] Time until institutionalization in this trial was 42 months for treatment participants and 28 months in the control group after an average of 7.7 years of followup.[361]

Other Interventions. Eight fair-quality trials examined other types of interventions aimed at caregivers or caregiver-patient dyads, which involved little to no general education about dementia or caregiving skills development. Three trials (n=293) counseled caregivers to increase physical activity, usually through home-based regimens.[326-328] Three trials (n=486) provided caregivers with peer support.[322-324] One additional psychoeducation trial included an arm targeting peer support (n=257).[325] One trial (n=50) conducted multidisciplinary assessments and treatment planning, including two intensive assessment sessions and one family conference with the patient, caregiver, and other family members.[329] None of these trials or comparisons showed a reduction in caregiver burden or depression outcomes. While one caregiver physical activity trial showed a 6-month reduction in perceived stress, this group difference disappeared at the 12-month followup.[326] Two caregiver physical activity trials reported dementia patient outcomes and found no group differences in patient behavior.[327,328] None of these trials reported on adverse effects.

Other Nonpharmacologic Interventions (Table 15, Figure 15)

We identified 32 trials (n=4,668) that evaluated nonpharmacologic interventions that targeted the patient, rather than the caregiver or patient-caregiver dyad. These interventions included: 1) cognitive training, rehabilitation, and/or stimulation, with or without motor skills training interventions (k=15; n=1,128); 2) exercise interventions (k=10; n=1,033); 3) multidisciplinary care interventions involving assessment and care coordination (k=5; n=1,766); and 4) education-only interventions (k=2; n=741). Many of these interventions targeted people with MCI or included people with MCI and dementia, including seven of the cognitive training or stimulation trials, six of the exercise trials, and one multidisciplinary care intervention. The remaining trials targeted people with mild to moderate dementia, who were usually identified as having AD. Two trials evaluating multidisciplinary care interventions were conducted in assisted living facilities. While the types of outcomes and duration of followup varied across trials, cognitive intervention and exercise trials primarily reported measures of cognitive function. These trials less commonly reported measures of physical function, HRQL, and depression, while multidisciplinary care intervention trials were less consistent in types of outcomes reported and also reported measures of institutionalization and hospitalization. Trials rarely mentioned harms.

Although the findings of the 15 cognitive intervention trials (n=1,128) were somewhat inconsistent, they generally support cognitive stimulation with or without cognitive training (k=6; n=513) to improve short-term global cognitive function (6 to 12 months) for people with MCI or dementia. Based on very sparse reporting of other outcomes, however, it is still unclear if this approach can improve other important outcomes, such as physical function, HRQL, or depression. The magnitude of benefit on global cognitive function, however, is also not clear given the very wide CIs and wide range of absolute mean differences on the ADAS-cog (0 to 13 points), ranging from clinically not meaningful to a large effect. Ten exercise intervention trials (n=1,033) did not find consistent benefit for global cognitive function outcomes, found no benefit on depression, and other outcomes (including physical function outcomes) were not

consistently reported. Although there is evidence of benefit in a few of the better-conducted trials, we are unable to determine if there is a clinically important benefit for exercise interventions on reported outcomes due to the limited number of trials and clinical heterogeneity of the populations, exercise interventions, and reported outcomes. We found no evidence of increased total or serious adverse effects due to exercise interventions among trial participants.

The limited number of exercise trials prevents us from determining the consistency and generalizability of this reported benefit. None the five trials evaluating multidisciplinary care interventions and neither of the two trials evaluating provider education-only interventions found benefits in cognitive or physical function, HRQL, or institutionalization. Cognitive and multidisciplinary care interventions did not report harms. Included trials found no evidence of increased total or serious adverse effects due to exercise interventions. Additionally, limitations in the primary evidence do not allow for any meaningful analyses of outcome findings by important patient subgroups. A brief summary of important study characteristics and reported outcomes is shown in **Table 15**. More detailed study characteristics and outcomes can be found in **Appendix E Tables 9–11** and **Appendix F Tables 8–11**.

Cognitive Interventions

Intervention Characteristics. Fifteen included trials (n=1,128) evaluated a variety of cognitive interventions, including cognitive training, cognitive rehabilitation, and/or stimulation with or without motor skills training interventions (**Table 15**).

Seven trials (n=486) were conducted exclusively or partially in people with MCI. Three of these seven trials evaluated cognitive training interventions in conjunction with relaxation or stress management training compared with a wait-list control group. These interventions included between five and 12 sessions.[380-383] The other three trials evaluated cognitive training plus cognitive stimulation interventions, which included between 20 and 104 sessions.[384-386] Two trials evaluated intensive interventions given in conjunction with psychomotor training compared with a minimally active control group.[384,385] Both of these trials were conducted in mixed populations of people with either MCI or dementia.

Eight trials (n=642) were conducted exclusively in people with dementia, the majority of which specified AD. Four of the seven trials evaluated cognitive training or cognitive rehabilitation interventions, which ranged widely in intensity from six to 120 sessions. These trials also included different cointerventions, including exercise, cognitive behavioral training, and stress management.[387-390] Two trials evaluated cognitive stimulation interventions; one intervention lasted eight sessions, the other included 260 sessions. These two interventions were compared with a wait-list or no intervention control group.[215,391] One trial evaluated a cognitive training and cognitive stimulation intervention that included six sessions compared with a wait-list control group.[392] One trial evaluated a unique intervention focusing on caregiver training, support, patient memory, and coping strategies.[393]

Population Characteristics. These trials were conducted in people exclusively with MCI (k= 5; n=363), people with MCI or dementia (k=2; n=123), or people exclusively with dementia (k=8; n=642). In one of the two trials with a mixed population, results were reported separately for

persons with MCI versus dementia.[384] The average age of patients in the MCI trials ranged from 68 to 74 years. The trial that included a population with the average age of 68 years was an outlier, as this population had lower education (conducted in Greece).[386] These trials included both men and women and were conducted in primarily white populations in the United States, Canada, Australia, and western Europe. The mean MMSE score ranged from 26.4 to 27.9.

The average age of patients with dementia ranged from 74 to 82 years. These trials included a good distribution of both men and women, but were conducted in mostly white populations in the United States and western Europe. Most trials only included patients with dementia who had AD. The mean MMSE score ranged from 20.8 to 25.1.

Study Characteristics. We rated all these trials as fair quality. In general, trials were relatively small (n<100), of limited duration (3 to 6 months followup), and conducted completers-only analyses.

Findings. While all trials reported some measure of cognitive functioning as an outcome, only 10 of the 15 trials reported global cognitive measures. The majority of the remaining trials reported memory-specific measures of cognitive function (**Table 15**). Isolated trials also reported outcome measures of physical function, HRQL, institutionalization, caregiver burden, or patient symptoms (most commonly depression). These results are only mentioned briefly, however, due to the sparse nature of these outcomes and concern of selective reporting.

Overall, cognitive training alone does not appear to improve global or memory-specific cognitive functioning at 3 to 6 months (**Table 15**). Only one trial reported global cognitive function; the remaining trials did not find any statistically significant difference in memory-specific cognitive outcomes at 3 to 6 months. However, it appears that cognitive stimulation with or without cognitive training in people with MCI or dementia can improve global cognitive function at 6 to 12 months. A meta-analysis of these trials (k=6; n=513) showed a moderate standardized effect size for global cognitive functioning favoring the intervention (-0.59 [95% CI, -0.93 to -0.25]; I^2=52.7%) (**Figure 15**). CIs were quite wide. Consequently, the effect on global cognitive functioning can range from small to large. The three trials that included cognitive stimulation reported a very wide range of differences in means, ranging from approximately 0 to 13 points on the ADAS-cog between the intervention and control groups.[215, 384,392] The two trials that used the MMSE had an approximate 1-point difference between groups.[386,387] The statistical heterogeneity was also quite high. One trial (n=84) in people with both MCI and dementia could not be included in the meta-analysis because of limitations in how the data were reported. This trial evaluated an intensive cognitive stimulation plus cognitive training intervention and found no statistically significant difference in ADAS-cog or MMSE scores at 12 months between the intervention group and a minimally active control group (**Table 15**).[385] There were important differences in the populations and interventions evaluated, as well as study design. Despite these differences, however, we cannot explain the differences in trial findings through MCI versus dementia, intervention intensity, or length of followup individually. The small number of trials limits our ability to determine if these or other characteristics are moderating the effects and effect sizes seen in these trials. Only one of the included trials (n=86) evaluated a cognitive stimulation intervention lasting 1 year, reported longer-term followup, and showed beneficial differences in cognitive improvement between the two groups that were still statistically

significant at 24 months.

Only one of the five trials that reported physical function outcomes found small but statistically significant improvement in physical function with a cognitive stimulation and training intervention in people with MCI, in addition to global cognitive function, at 6 months (**Table 15**).[386] Likewise, two of the eight trials that reported depression outcomes found small but statistically significant improvement. These trials did not find improvements in global cognitive function with cognitive stimulation and training interventions in people with MCI or dementia at 6 and 12 months (**Table 15**).[384,385] However, these and other outcomes (i.e., HRQL, institutionalization, neuropsychiatric disturbances, and caregiver burden) were sparsely reported. As such, the interpretation of these outcomes should not be in isolation of the primary outcome findings for each of these trials. None of these included trials reported on harms.

Exercise Interventions

Intervention Characteristics. Ten included trials (n=1,033) evaluated a variety of exercise interventions, including aerobic training, strength/resistance training, balance training (or some combination of the three), or Tai Chi (**Table 15**).

Six trials (n=783) were conducted exclusively in people with MCI. These trials evaluated different interventions (self-guided or guided exercise). Two trials (n=444) evaluated Tai Chi interventions.[394,395] One was conducted in the United States and the other in Hong Kong. Shorter trials had fully- or partially-guided exercise interventions that occurred one to four times weekly.[212,394,396,397] The longest trial evaluated a self-guided exercise intervention occurring three times a week for 18 months. All of these trials included an active control group in which people received stretching, balance, relaxation exercises, or nonexercise educational materials.

Four trials (n=250) were conducted exclusively in people with dementia, three of which specified AD. All trials generally included aerobic and/or strength training. Three of the four trials evaluated a self-guided intervention.[337,398,399] Three trials included an active control in which people received nonexercise-based interventions, and one trial used a wait-list control group.[399]

Population Characteristics. The average age of patients in the MCI trials ranged from 69 to 79 years. While these trials included both men and women, one trial was conducted exclusively in women.[397] Trials were conducted in the United States, Canada, Australia, Japan, and Hong Kong. The mean MMSE score ranged from 24.5 to 26.8. The trial in Hong Kong was conducted in generally older people with a lower education level, which might explain the low MMSE score for people with MCI.[394] The average age of patients with dementia ranged from 74 to 84 years. These trials were conducted in primarily white populations in the United States, Italy, and Australia. Three trials only included patients with AD.[398,400] The mean MMSE score ranged from 16.7 to 22.0.

Study Characteristics. We rated all but one of these trials as fair quality. Common limitations in quality for this body of literature included: differences in baseline characteristics, small sample sizes, relatively short followup, limited reporting, and completers-only analyses.

Findings. Included trials reported either measures of cognitive or physical functioning as the primary outcome. Seven of these trials reported global measures of cognitive function,[212,213,394,395,398,399,401] two of which reported memory-only measures[396,397] and three of which reported measures of physical functioning (**Table 15**).[399-401] Five trials also reported measures of depression[213,394, 398-400] and four trials reported on adverse effects.[213,397,398,401] Other outcomes of HRQL, institutionalization, hospitalization, neuropsychiatric disturbances, and caregiver burden were not commonly reported.

Overall, the exercise trials showed no benefit on outcomes of cognitive function for people with MCI or dementia; however, findings from these trials were inconsistent. Inconsistent findings of benefit are possibly due to the heterogeneity in populations and interventions studied. For MCI, four of the six trials showed no significant effects on cognitive outcomes, three of which used measures of global cognitive function. Two trials (n=444) evaluated a Tai Chi intervention in older adults with a relatively low mean MMSE score for MCI.[394,395] Two trials (n=220) found a very small benefit in global cognitive function (about 1 point on the MMSE or ADAS-cog) at 12 to 18 months for people in the multicomponent exercise arm.[212,213] Only two trials reported on harms and found no difference in total adverse events between the treatment and control groups.[213,397]

Likewise, findings in people with dementia were inconsistent among the four included exercise trials. One small trial (n=27) conducted in the United States evaluated a self-guided aerobic, strength, and balance training intervention versus home safety assessment and found no benefit in cognitive function, HRQL, symptoms, or caregiver burden at 3 months (**Table 15**).[398] Two small trials (n=70) found a statistically significant benefit in both cognitive and physical functioning outcomes for the exercise group versus a nonexercise active control in the short-term (3 to 4 months).[399,401] One good-quality trial (n=153) conducted in the United States evaluated an exercise plus caregiver education and skills training intervention versus usual care and found a clinically and statistically significant benefit in physical function and HRQL, but not institutionalization or depression symptoms, at 18 months (mean difference in Sickness Impact Profile (SIP) score, 8.1 [p=0.02]; mean difference in Short-Form Health Survey (SF-36) score, -15.9 [p<0.01]).[400] Two of these four trials reported no difference in total or serious adverse events between treatment arms.[398,401]

Multidisciplinary Care Interventions

Intervention Characteristics. We included five trials (n=1,766) of multidisciplinary care interventions that involved some aspect of assessment and care coordination. Each of these five trials evaluated different interventions (**Table 15**, **Appendix E Table 11**). The first trial (n=100), the only one conducted in the United States, evaluated four multidisciplinary assessments in residents of an assisted living facility versus medical evaluation by the resident's primary care physician.[402] This intervention's primary aim was to reduce unexpected transitions of care. The other interventions were delivered through specialty care clinics. One trial (n=230) conducted in the Netherlands evaluated a one-time multidisciplinary assessment with recommendations sent to the patient's general practitioner versus usual care. Another trial (n=130) conducted in the Netherlands evaluated an assessment and management intervention delivered through a neurologist or geriatrician that focused on optimizing vascular care (using ASA, vitamin B6,

folate, HMG-CoA reductase inhibitors, and, if indicated, therapies targeting blood pressure, glucose, smoking, and diet/activity) in patients with AD (not VaD) versus usual care delivered through general practitioners.[403] Two well-conducted trials (n=1,306), one in France and one in the Netherlands, evaluated a multidisciplinary assessment and management intervention delivered through memory clinics, with ongoing consultations that involved the caregiver, using guidelines/protocols for management of care versus usual care.[404,405]

Population Characteristics. All trials were conducted in people with dementia. While one trial (n=230) stated that it included people with both MCI and dementia, the mean MMSE score in this trial was only 20.2. As such, we discuss this trial with the other trials focusing exclusively on people with dementia. The average age of patients ranged from 76.5 to 82.2 years (**Table 15**). Trials included both men and women and were conducted in primarily white populations in the United States, the Netherlands, and France. Only two trials specified that patients had AD.[403,404] The mean baseline MMSE score ranged from 14.8 to 22.7. One trial conducted exclusively in residents of an assisted living facility in the United States had the lowest average MMSE score.[402]

Study Characteristics. Only one trial was rated as good quality; the other four were rated as fair quality and had at least one major limitation, including high attrition (>20%), evidence of attrition bias, or nonblinded assessment of outcomes.

Findings. Outcome measures varied across trials due to the different types and aims of these interventions. Overall, none of the trials (n=1,766) demonstrated a benefit in people receiving the multidisciplinary intervention (**Table 15**). None of the trials specifically mentioned harms. The trial conducted in U.S assisted living facilities (n=100) aimed at decreasing unexpected transitions of care found no difference in institutionalization, hospitalizations, or ED visits between intervention and usual care groups at 9 months.[402] The other three trials evaluating assessment plus or minus management interventions (n=1,666) showed no benefit in global cognitive or physical functioning, HRQL, institutionalization, or patient symptoms at 12 to 24 months.[403-406] While two trials evaluated similar multidisciplinary interventions that included the caregiver, only one of these trials reported any caregiver outcomes.[405] This trial reported statistically significant benefits in caregiver depression and anxiety, but not overall caregiver HRQL or distress, in the intervention group compared with usual care at 12 months.

Education-Only Interventions

Two fair-quality trials (n=741), one in Australia and one in Germany, evaluated educational interventions aimed at residential care staff and/or general practitioners caring for people with dementia (**Table 15**).[407,408] In both interventions, residential care staff and/or general practitioners received intensive education across a variety of topics, such as dementia and delirium, concerning behaviors, pain management, personal care and activities, communication with patients and family, medical treatment options, caregiver counseling, and effective working between general practitioners and residential care facilities. Patients in one trial were all permanent residents of residential care facilities and were quite old (mean age, 85.3 years), with a fairly low median MMSE score (approximately 11).[407] In the other trial, patients were from general practitioner practices in Germany, with a mean age of 80 years and a mean MMSE score

of 18.7.[408] These cluster RCTs were generally well-conducted but of fair quality, as they both had suboptimal followup (<80%), and one also had evidence of attrition bias.[407] In addition, they either reported low adherence to the educational intervention or did not report adherence.

The trial conducted in residential care facilities showed no statistically significant differences in any of the reported outcomes, including HRQL (as rated by the patient, staff, or next of kin), neuropsychiatric disturbances, or proportion of people hospitalized at 30 days, between education groups and control groups at 6 months.[407] The other trial, in general practitioner practices, showed no statistically significant differences in its primary outcome of time to institutionalization between groups at 24 months.[408] Neither of the two trials specifically mentioned harms.

Chapter 4. Discussion

Summary of Findings

Overall

We did not identify any direct trial evidence demonstrating that screening for cognitive impairment improves health outcomes or important patient, family, or clinician decisionmaking outcomes. As such, our review primarily addressed two broad questions: 1) How well does screening detect dementia or MCI in primary care? and 2) How effective are interventions to improve patient or caregiver outcomes in people with screen-detected cognitive impairment (i.e., those with mild to moderate dementia or MCI)? Our review identified a very large body of well-conducted diagnostic accuracy studies that evaluated brief screening instruments in unselected older adults outside of specialty care (i.e., memory or neurology clinics). Despite this large number of studies, however, only a handful of instruments have been studied in more than one trial applicable to primary care (**Table 16**). Nonetheless, it is clear that several brief instruments can have sensitivity and specificity greater than 80 percent to detect dementia, regardless of etiology (e.g., AD vs. VaD). The MMSE (k=25) is the best-studied instrument; however, it has the longest administration time (up to 10 minutes) and is not available for public use (without cost). Other instruments with more limited evidence include the CDT (k=7), Mini-Cog (k=4), MIS (k=5), AMT (k=4), SPMSQ (k=4), FCSRT (k=2), 7MS (k=2), TICS (k=2; also not available for public use), and IQCODE (k=5). However, the AMT, SPMSQ, FCSRT, 7MS, and TICS have very limited evidence (only one study each) in English. Each of these instruments can have reasonable test performance; however, estimates of sensitivity and specificity vary, and the optimal diagnostic threshold/cut-point for many of these instruments is unclear. While other instruments appear promising, such as the 6-Item Screener, VAT, GPCOG, ADLs/IADLs, Benton's Orientation Test, Delayed Recall Test, and Short Concord Informant Dementia scale, they have only been studied once in primary care–relevant populations. No studies directly address the adverse psychological effects of screening or adverse effects from false-positive or false-negative testing. One fair-quality study found that approximately half the older adults who screened positive for cognitive impairment refused to complete a formal diagnostic workup.

Our review identified a very large body of well-conducted trials examining the efficacy and effectiveness of a broad range of interventions aimed at either the patient or the caregiver. However, none of these trials examined the ability of interventions to change decisionmaking of the patient, caregiver/family, or clinician. Currently, the two most developed bodies of intervention literature address FDA-approved medications to treat AD and psychoeducational caregiver interventions. These types of interventions appear to have benefit in people with moderate dementia; however, the clinical importance of this benefit and the degree to which it might apply to older adults with screen-detected cognitive impairment is uncertain. AChEIs and memantine can improve global cognitive function and AChEIs can improve global function in the short-term for people with moderate AD. Much more limited evidence exists for people with mild AD or other types of dementia. The average effects of changes in cognitive functioning observed in trials, however, are small and the clinical importance is likely negligible when using commonly accepted thresholds to interpret this change. While clinically important benefits may

exist for targeted individuals, trials included in our review did not distinguish which individuals would most likely benefit. Likewise, complex interventions aimed at caregivers and patient-caregiver dyads (including case management, caregiver support interventions) can improve caregiver burden and depression, but the average effects of benefit in these trials are small and the clinical importance of these small changes on outcome measures remains unclear. Based on more limited evidence, cognitive stimulation can also improve (or prevent decline of) global cognitive function. A very wide 95 percent CI, however, limits our ability to determine the magnitude of benefit. Inconsistent reporting also limits our ability to interpret the effect of these pharmacologic and nonpharmacologic interventions on other important patient outcomes (e.g., HRQL). Discontinuation of AChEIs is common, and serious harms of AChEIs can include central nervous system, cardiovascular, and gastrointestinal signs and symptoms. Harms were not reported for caregiver interventions or cognitive stimulation, but are assumed to be minimal.

A much smaller, and newer, body of literature examines the test performance of various screening instruments and the effectiveness of various interventions for MCI (**Table 16**). These studies generally used different diagnostic criteria to identify MCI, and none of the studies used the most recent criteria as defined by the National Institute on Aging-Alzheimer's Association. The diagnostic accuracy of these instruments (i.e., CDT, Mini-Cog, TICS, MMSE, MoCA, and IQCODE) in primary care–relevant populations suggest they have much lower sensitivity to detect MCI than dementia, despite adjustment of diagnostic thresholds/cut-points. The AD8, FOME, SLUMS, and CAMCI are all promising instruments, although their test performances have not yet been reproduced in unselected populations. Currently, the benefit of AChEIs, memantine, and cognitive stimulation on global cognitive function and other important outcomes remains uncertain for people with MCI due to the small evidence base with mixed findings.

Screening

Our review identified a number of brief instruments that primary care providers can use to screen for cognitive impairment (**Table 16**). The MMSE is the best studied of these instruments; pooled estimates across 14 studies (n=10,185) resulted in 88.3 percent sensitivity (95% CI, 81.3% to 92.9%) and 86.2 percent specificity (95% CI, 81.8% to 89.7%) for a cut-point of 23/24 or 24/25. Using higher cut-points (k=3; n=1,544) did not improve sensitivity to detect MCI. Researchers have also studied other instruments, including the CDT, Mini-Cog, MIS, AMT, SPMSQ, FCSRT, 7MS, TICS, and IQCODE, although this research is less extensive. Based on these studies, the CDT (k=7; n=2,509) had a much wider range of sensitivity and specificity (67% to 97.9% and 69% to 94.2%, respectively), and the optimal cut-point was unclear in the body of literature we examined. The Mini-Cog (k=4; n=1,570) likely has better sensitivity than the CDT alone (76% to 100%), but with a possible tradeoff of lower specificity (54% to 85.2%). For MCI, the CDT (k=4; n= 4,191) and Mini-Cog (k=3; n=1,092) clearly have much lower sensitivity. Although the MIS (k=5; n=1,971) and AMT (k=4; n=824) can have relatively good test performance to screen for dementia, sensitivity in the best-quality studies was very low (~40%). The SPMSQ (k=4; n=1,057), FCSRT (k=2; n=734), TICS (k=2; n=677), and 7MS (k=2; n=553) also have reasonable test performance to detect dementia, although this is based on a very limited number of studies and unknown optimal cut-points for each instrument. If an informant-based screening tool is desired, the IQCODE may be a reasonable option to screen for dementia (k=5; n=1,251), although the optimal cut-point is unclear. There is less evidence to support its use to

detect MCI (k=4; n=975). The majority of the diagnostic accuracy studies did not specify what types of dementia were identified, although the majority of cases were presumed to be AD. Only five studies addressed screening for specific types of dementia and none of them reported the test performance separately for each type of dementia.[171,172,174,175,197] One included study by Borson and colleagues found that the percent of cases correctly identified by the Mini-Cog was 99 percent of AD cases, 100 percent of VaD cases, and 82 percent of other dementia cases.[172]

Our review findings for the diagnostic accuracy of screening for dementia are generally consistent with other recent existing reviews.[2,19,186,409] Our review includes twice the number of studies as the most comprehensive existing reviews.[19,409] Our review, however, excludes many studies that were included in these prior reviews because we were more stringent on the internal validity (i.e., we excluded studies without a true reference standard or with significant verification bias, case-control studies, or generally poor-quality studies) and external validity (i.e., we excluded studies evaluating lengthy instruments not feasible in primary care, or studies conducted in memory clinics or other specialty care or referred populations). The previous systematic review conducted for the USPSTF included a more limited body of evidence and somewhat more selective literature, which was less applicable to populations in primary care.[2] This review found the most robust evidence for the MMSE, and that depending on the cut-point, sensitivity and specificity was approximately 91 to 92 percent and 56 to 96 percent, respectively. This review acknowledged the well-recognized differences in test norms based on age and education, although there is no commonly accepted (standardized) cut-point adjustment by age and education. A subsequent review by Holsinger and colleagues for the Rational Clinical Exam series updated the USPSTF review to 2006.[19] This review had similar findings for the MMSE and found that a few other instruments had reasonable test performance, including the MIS, AMT, CDT, 7MS, and GPCOG; however, all findings were based on very limited studies.[19] It found that the MIS had the best test performance (likelihood ratio), but was evaluated in only one study.[19] Another recent review by Brodaty and colleagues, through January 2004, found similar commonly evaluated instruments, including the CDT, Mini-Cog, MIS, AMT, MMSE, and IQCODE.[409]

This review found that the GPCOG, Mini-Cog, and MIS performed better than the MMSE; however, this is based on only one study evaluating each instrument.[409] One review, focused exclusively on the MMSE, estimated sensitivity and specificity at 78.4 and 87.8 percent (CIs not reported), respectively.[76] While these estimates fall within our range of estimates, we caution overemphasizing the pooled estimates given the clinical heterogeneity across studies (i.e., differences in populations and cut-points).[76] One review specifically addressed the differential ability of the various cognitive screening instruments to detect the different types of dementia.[186] Because many of the instruments focus preferentially on memory dysfunction (as opposed to other domains of cognitive function), which is the hallmark of AD, but is not necessarily impaired at an early stage with other types of dementia, it is thought that some instruments may perform better (or more consistently) across different types of dementia. This review found that the instruments that rated the "highest" with regard to validation methods, reliability, test performance, and coverage of key cognitive domains included the MMSE and instruments that expand on the content of the MMSE (from which an MMSE score can be derived). The authors concluded that despite an understandable drive toward ultra-brief tests which can be used in a typically time-constrained general practitioner consultation, an administration time of more than

10 minutes appears to be an unavoidable cost of achieving sufficiently robust statistical performance while covering key domains.[186]

Screening for cognitive impairment may have direct or indirect harms from the diagnostic inaccuracy of screening (false-positives and false-negatives). However, we found no studies to substantiate or refute the concern about harms of screening. We included only one small fair-quality study that addressed harms, which found that the refusal rate for subsequent diagnostic assessment can be very high, suggesting patient issues with subsequent testing or diagnostic confirmation of screening results; however, this study did not directly assess psychological harms.[206,207] Studies not included in our review suggest that patients with dementia, even if upset with their diagnosis, wanted to know their diagnosis,[410] and that willingness to participate in screening is directly associated with perceptions about the benefits of screening.[411] Although screening itself, and the subsequent diagnostic workup for abnormal results, is generally noninvasive, there may still be significant harm from false-positives if patients or clinicians do not follow through with subsequent diagnostic testing. Thus, if false-positives are a concern, instruments (or cut-points) with very high specificity should be given preference. Potential harms from false-negatives, if they are of concern, can be minimized with repeated screening.

Treatment

Our review was not a comprehensive analysis of all treatment and management options for people with cognitive impairment; instead, we focused on selected interventions aimed at people with mild to moderate dementia and/or MCI (i.e., those populations more representative of screen-detected older adults with cognitive impairment). We reviewed currently available pharmacologic interventions in the United States, including: 1) FDA-approved medications for use in AD, namely AChEIs and memantine (although memantine is currently approved for use in patients with moderate to severe AD, we included only those trials evaluating this medication in our population of interest); 2) potentially disease-modifying medications (i.e., antiplatelet therapy, antihypertension therapy, HMG Co-A reductase inhibitors, NSAIDs, gonadal steroids); and 3) potentially disease-modifying vitamins or supplements, not including herbal supplements (e.g., gingko biloba). Nonpharmacologic interventions covered in this review include: 1) focused and complex interventions aimed primarily at the caregiver or patient-caregiver dyad; and 2) focused and complex interventions aimed primarily at the patient (i.e., interventions to support or enhance cognitive function and/or physical function, education, and multidisciplinary care interventions involving assessment and care coordination).

Overall, based on a large body of evidence, including one systematic review of 50 RCTs and 14 subsequently published RCTs, AChEIs and memantine can improve global cognitive function in the short-term (average effects of 1- to 3-point change on the ADAS-cog) (**Table 16**). The vast majority of evidence is from trials in people with AD and with followup limited to 6 months. Using commonly accepted values to interpret the clinical importance of these changes (i.e., 4-point change in ADAS-cog over 6 months), it appears that the average effect of these changes may not be clinically important. The prediction interval for the pooled analyses on ADAS-cog outcomes usually crossed into statistical nonsignificance for each of these medications, indicating the statistical significance of the pooled effect may not be robust to the addition of new trials (data not shown). The prediction interval gives the upper and lower bounds of the true

effect in 95 percent of cases of a new (yet unpublished/not conducted) study, assuming the same level of statistical heterogeneity. Measures of global functioning (e.g., CIBIC-plus) were less commonly reported, but were still reported in the majority of trials. AChEIs appear to consistently improve measures of global functioning in people with AD in the short-term, but memantine does not. Although the CIBIC-plus is inherently a clinically relevant measure of function, and as a result any change in score is generally considered clinically important, improvement in trials were less than 1-point change (a fraction of a point on a 7-point scale). Only seven trials and eight OLEs of included trials had longer-term followup that demonstrated similar effects of benefits for AChEIs but not memantine compared with 6-month followup from trials. Two trials of donepezil in people with MCI showed no difference in progression to AD at about 3 years. Outcome measures of overall physical function were not commonly reported, and these measures showed mixed results when they were reported. Therefore, it is unclear what impact these medications have on global physical functioning given the inconsistent reporting and findings.

Our review findings update the large body of evidence summarized by Raina and colleagues.[110] Findings from published trials since this review are entirely consistent with Raina's findings for AChEIs and memantine, with the largest addition of evidence for rivastigmine. Findings from trials of memantine published after this review are less consistent, as findings from three additional trials in people with mild to moderate dementia did not show a benefit in global functioning,[224-226] in contrast to the small benefit in global functioning observed in the five trials included in the review by Raina and colleagues. Our review's findings on the benefit and magnitude of benefit are also consistent with evidence that supports the March 2011 NICE guidelines on the use of donepezil, galantamine, rivastigmine, and memantine for the treatment of AD. This evidence also included a wider range of studies, including comparative effectiveness trials, open-label studies, observational studies of effectiveness, and unpublished data submitted by pharmaceutical companies.[412] In addition to our review findings, the NICE guideline included evidence to suggest that: 1) based on observational studies, cognitive benefits from donepezil can be maintained for up to 3 years; 2) based on a single RCT, rivastigmine had a significant difference in improvement of global outcomes but not cognitive function compared with donepezil; and 3) based on mixed treatment comparison using Bayeseian Markov chain Monte Carlo sampling, AChEIs provided benefits for cognitive function, as well as physical function (as measured by ADLs). Finally, evidence for these medications in people with MCI is much more limited (k=5). While these trials show a small statistically significant benefit for donepezil and galantamine (but not memantine) on global cognitive function, the magnitude of this effect is likely not clinically meaningful. Our review's findings are consistent with a recent Cochrane review of AChEIs for MCI, which found no difference from placebo for progression to MCI at 1 and 3 years.[413]

Based on 66 RCTs, six OLEs of included RCTs, and 13 other observational studies, it is clear that AChEIs and memantine have adverse effects (**Table 16**). Discontinuation due to adverse effects from AChEIs was higher in treatment groups compared with placebo groups, but this trend was not apparent for memantine. While there did not appear to be an increase in serious adverse events (excluding tacrine) in trials with selected populations and limited duration of followup, the estimates of total serious adverse events for AChEIs in one observational study were higher than proportions of serious adverse events observed in trials. From observational

studies, AChEIs increase the risk for bradycardia and falls, syncope, and pacemaker placement due to bradycardia. Due to resource limitations, our review did not report the proportion of specific types of adverse events or side effects and did not search the FDA databases for additional harms not reported in published studies. Types and relative frequencies of specific adverse effects are well described in narrative reviews and pharmacologic references. The most common adverse reactions for AChEIs include gastrointestinal symptoms (i.e., nausea, vomiting, diarrhea, anorexia, and abdominal discomfort), central nervous system symptoms (i.e., dizziness, headaches, sleep disturbance, somnolence, confusion, fatigue, depression, and other mood or neuropsychiatric disturbances), and cardiovascular signs/symptoms (i.e., bradycardia, hypertension, syncope, and chest pain).[414-416] The most common adverse reactions for memantine include gastrointestinal symptoms (i.e., constipation, vomiting), central nervous system symptoms (i.e., dizziness, headaches, somnolence, confusion, fatigue), and cardiovascular signs (i.e., hypertension).[417] An older review from 2006 by Hansen and colleagues was conducted as part of the Drug Effectiveness Review Project.[418] This review, designed to evaluate the effectiveness and comparative effectiveness of these medications, included a hand search of the Center for Drug Evaluation and Research database to identify unpublished research submitted to the FDA and dossiers submitted by pharmaceutical companies. Neither of these sources contributed any unpublished evidence on harms for currently used medications (excluding tacrine).[418]

We found 26 RCTs that evaluated other medications or supplements, including low-dose aspirin, HMG-CoA reductase inhibitors (simvastatin and atorvastatin), NSAIDs (ibuprofen, naproxen, indomethacin, and celecoxib), gonadal steroids (estrogen plus or minus progesterone and testosterone), and dietary supplements (multivitamins, B vitamins, vitamin E plus or minus vitamin C, and omega-3 fatty acids). However, we found no trials evaluating antihypertension therapies that met our inclusion criteria. We found no benefit on global cognitive or physical function in people with mild to moderate dementia or MCI for any of these medications or supplements (**Table 16**). Our review's findings for these medications are consistent with other existing reviews for HMG-CoA reductase inhibitors,[419,420] aspirin and NSAIDs,[421] gonadal steroids,[422] B vitamins,[111-115,423,424] vitamin E,[425] and omega-3 fatty acids.[115,116]

We found that complex psychoeducational interventions aimed at caregivers or dyads (k=52) have a small benefit on caregiver burden and depression outcomes based on a large body of literature that evaluated nonpharmacologic interventions. While there were substantial clinical differences (and statistical heterogeneity) among interventions, these interventions generally provided education about dementia and/or caregiving, caregiver skills training, and formal mechanisms of support. Interpretation of the standardized effect sizes and their 95 percent CIs range from very small (about 0.1) to small (about 0.3), which represented a 0- to 5-point change on the Zarit CBI (88-point scale) or 2- to 5-point change on the CES-D (60-point scale). Furthermore, prediction intervals for the pooled analyses on caregiver burden and depression outcomes indicate the statistical significance may not be robust to the addition of new trials (data not shown). Unfortunately, inconsistent reporting of other self-reported outcomes (e.g., global stress or distress, anxiety, HRQL, self-reported health status) and institutionalization limits our ability to interpret the clinical importance and consistency of findings for these outcomes. None of the included trials reported harms. We did not identify any additional studies that explicitly evaluated harms of caregiver interventions.

Our review is generally, but not entirely, consistent with existing systematic reviews on caregiver interventions, including case management interventions. Existing systematic reviews varied in the trials they included, with slight differences in focus and inclusion criteria. Nonetheless, existing reviews generally found that caregiver or dyad interventions (including caregiver support and case management) could improve caregiver burden (or well-being) and depression. These reviews lacked evidence for delaying institutionalization.[98,426-429] Magnitude of effect on caregiver outcomes varied slightly due to differences in included trials and definitions of outcomes; however, effect sizes were generally small to moderate, with 95 percent CIs inclusive (consistent) with our review findings. Differences in findings of benefit on institutionalization are due to differences in included trials, based on our review's exclusion criteria (exclusion of people with moderately severe to severe dementia, respite care interventions, and trials without a true control or usual care group). Our review included a larger number of trials than other reviews, with 21 interventions aimed at the caregiver or dyad reporting institutionalization, only one of which showed statistically significant differences in institutionalization between trial arms.[361]

Based on a subset of trials (k=6; n=513) evaluating cognitive interventions, cognitive stimulation with or without cognitive training can improve global cognitive function in persons with MCI or dementia at 6 to 12 months. However, the statistical heterogeneity among trials and imprecision of the estimate (very wide 95% CI) was large. Given the relatively small sample size and high statistical heterogeneity, the prediction interval for the pooled analyses on global cognitive outcomes was not statistically significant (data not shown). Therefore, although promising, the certainty and magnitude of effect of cognitive stimulation in people with mild to moderate dementia or MCI is still unclear based on our review's findings. Findings from existing systematic reviews evaluating cognitive interventions were generally consistent with our review findings, although our conclusions based on these findings are a bit more understated.[430-432] A recent Cochrane review by Woods and colleagues found these interventions (k=15; n=718) consistently improved global cognitive function (SMD, 0.41 [95% CI, 0.25 to 0.57]; I^2=0%). This review differed from our review in its focus on persons with mild to moderate dementia, exclusion of institutionalized individuals, and differences in outcome analyses.[430]

Although there was no consistent benefit observed for exercise interventions (k=10; n=1,033), three of the better-conducted trials suggest a benefit in global cognitive function in people with MCI or physical functioning and HRQL in persons with dementia at 12 to 18 months. Overall, the clinical impact of exercise in people with impaired cognitive function is unclear, due to the limited number of trials and variation in populations, interventions, and reported outcomes. Our review's sparse and mixed findings were consistent with another existing systematic review's findings in noninstitutionalized older adults with dementia.[433]

Applicability of Findings to Practice

Implementation of Screening

Our review included brief screening instruments that could be reasonably administered in primary care (i.e., before, during, or after visits) by a clinician or primary care staff with minimal training or self-administered by the patient or a close informant. While most of the included

instruments are available in the public domain, the MMSE (which remains the best-studied instrument) and the TICS (an instrument designed to be delivered by telephone) are two notable exceptions. The cost of the instrument is likely a significant barrier to its implementation given other, albeit less well-studied, alternatives. The opportunity cost of screening can be minimized by choosing very brief instruments or those that can be self-administered. However, we acknowledge that there are implications for the subsequent workup of people with screen-detected impaired cognitive function, including issues around guidance on best practices for satisfactory diagnostic workup, resources and capacity for neuropsychological testing or referral to neurology, psychiatry, or geriatric specialty services (if needed), and the potential for refusal of diagnostic workup and issues around acceptability of further testing and the diagnosis itself.

The Patient Protection and Affordable Care Act of 2010 introduced an Annual Wellness Visit, as part of Medicare, which requires an assessment to detect cognitive impairment. Currently, while CMS does not prescribe any standardized cognitive assessment instrument, it is currently working with others (i.e., National Institute on Aging) on potential recommendations for use of specific instruments.[434] In addition, the Alzheimer's Association convened a workgroup to develop recommendations on how to operationalize the Annual Wellness Visit cognitive impairment assessment. This group recently outlined a stepwise approach and recommends the use of specific instruments (GPCOG, Mini-Cog, MIS, AD8, or short IQCODE; alternate tools, including the MMSE, SLUMS, or MoCA, at discretion of the clinician) in people at high risk for or those who have suspected cognitive impairment based on clinician observation, self- (or informant) reported concerns, and review of a Health Risk Assessment that includes questions on subjective cognitive complaints, ADLs, and IADLs. This approach is essentially a two-step screening process: screening with an assessment of ADLs/IADLs and a question on cognitive complaints, followed by a brief instrument designed to assess cognitive impairment. We found no evidence to support or refute this proposed method. Specifically, we found no diagnostic accuracy studies examining a two-step screening approach as described. Furthermore, our review focuses on screening, and therefore did not address the implementation of brief cognitive instruments in people with observed deficits or self-reported concerns (i.e., case-finding). Therefore, this review does not address implementation of testing in people with self-reported subjective memory complaints or known impaired ADLs or IADLs, although these instruments were included as cognitive screening instruments. Expert guidelines, including those of the USPSTF, have consistently recommended that all these people be assessed for cognitive impairment.[1,82,83,103,434] It makes clinical sense to identify risk factors or risk assessments to identify people at high risk for cognitive impairment. Other groups (i.e., Centers for Disease Control and Prevention, National Institute on Aging), in addition to the Alzheimer's Association Medicare Detection of Cognitive Impairment Workgroup, are working to determine how best to identify these populations for targeted screening (M. Wagster, oral communication, May 2012). This was beyond the scope of our report.

Age at Which to Start (and Stop) Screening (Table 17)

Age is the biggest risk factor for cognitive impairment. Therefore, if screening is advisable, then using age to target cognitive screening is a reasonable strategy. While population estimates vary, the best estimates for dementia prevalence in North America are generally low (<5%) before ages 70 to 75 years.[5,22] Prevalence of dementia increases with each decade of life. Between ages

70 to 75 years and 80 to 85 years, dementia prevalence ranges from about 5 to 20 percent. Dementia prevalence is quite high at age 80 or 85 years and older (>20%).[5,22]

The prevalence of dementia greatly affects the positive predictive value (PPV) of testing and therefore can be used to infer reasonable ages at which to start screening for cognitive impairment or possibly target subpopulations in which it could be reasonable to start earlier screening, if advisable (**Table 17**). Looking across a range of sensitivities and specificities representative of currently available brief cognitive screening instruments (based on our review), it appears that the PPV is greater than 50 percent if the prevalence of underlying dementia approximates 15 to 20 percent. The general prevalence is much lower in populations younger than age 75 years, as are the PPVs across a range of sensitivities and specificities. If screening is advisable, there is no compelling rationale to stop screening based on increasing prevalence with age. Therefore, the rationale for stopping screening should be based on evidence that intervening in the oldest old (age 85 years and older) does not improve important outcomes or the harms of intervening outweigh the potential benefit. Our review does not support or refute this idea. Arguably, cognitive screening in the oldest old may be considered case-finding as opposed to true screening, as the prevalence of memory complaints is extremely high in this group.[5]

Screening Interval

At a population level, the timing and frequency of rescreening is partly dependent on the incidence of dementia and the test performance of the cognitive screening instrument (i.e., rescreening can improve the sensitivity to detect dementia). Overall, there is a wide range of incidence rates. The incidence rate of AD grows exponentially with age, and the estimated doubling time of AD incidence in North America is 6 years.[435,436] Incidence rates from one U.S.-based longitudinal cohort study demonstrate that rates increase with age, from 11.7 cases per 1,000 person-years at ages younger than 75 years to 32.0 cases per 1,000 person-years at ages 75 to 79 years, 57.5 cases per 1,000 person-years at ages 80 to 84 years, and 95.9 cases per 1,000 person-years at age 85 years or older.[437] The incidence of dementia continues to increase with age even in the oldest old. A population-based longitudinal study of individuals age 90 years and older who did not have dementia at baseline found an overall incidence rate of dementia of 18.2 percent per year, for both men and women.[438]

If screening is advisable, based on incidence alone, it is reasonable to offer repeated screening, such as annually, and it may be reasonable to increase the frequency of repeated screening with increasing age (or other risk factors), such as more frequent screening in the oldest old (age ≥85 years), based on the very high incidence of dementia in this group. Repeated screening will also improve the cumulative sensitivity to detect dementia. Therefore, it may be reasonable to choose an instrument or scoring/cut-point for a particular instrument with very high specificity (e.g., >90%) at the expense of a slightly lower sensitivity, knowing that with repeated screening over time, the cumulative sensitivity will be much higher. Thresholds for acceptable levels of sensitivity and specificity, and therefore choice of instrument and cut-points, may vary depending on the stakeholder's resources and preferences.

Impact of (Early) Diagnosis on Decisionmaking

We found no direct trial evidence to address if screening altered patient or clinical decisionmaking. We searched for existing systematic and narrative reviews on this topic to understand the impact of earlier diagnosis (through screening) of dementia, as we were unable to find trial evidence. We found one comprehensive and relevant review in the 2011 World Alzheimer's Report.[439] Prince and colleagues attempted to answer if early diagnosis of cognitive impairment benefits people with dementia or their caregivers. Despite an extensive search, the authors found only three observational studies and five consensus statements or practice guidelines that addressed the impact of timing of diagnosis on subsequent disease course and outcomes for people with dementia and their caregivers. One large, observational study suggested that shorter time between first symptoms and first visit to a memory clinic was associated with longer patient survival. This study, however, had numerous limitations: 1) the onset of symptoms was assessed by retrospective recall by patients or relatives at the first visit to the clinic, 2) it is unclear if all important confounding variables were considered and controlled for, and 3) the representativeness of patients in this cohort is unclear, as they were all referred to a tertiary care center. Two additional observational studies attempted to determine the impact of early diagnosis on the subsequent rate of cognitive decline; both studies were relatively small, conducted in referral populations, and had methodological limitations. Despite a lack of empirical evidence, expert consensus statements and guidelines clearly believe that early diagnosis positively impacts important decisionmaking that ultimately will lead to improved patient outcomes and reduced future costs.[439] Expert opinions and narrative reviews state that early detection of cognitive decline may be beneficial because it can positively affect one or more of the following: 1) optimizing current medical management (e.g., ability to search for potentially treatable or reversible disorders, factor in patient comprehension and compliance of treatment plans and other conditions, avoid medications with anticholinergic effects, and better manage related symptoms, such as depression and irritability); 2) relief gained from better understanding of symptoms (e.g., greater patient and family understanding and awareness of, and therefore ability to adapt to, diagnosis of dementia); 3) maximizing decisionmaking autonomy and planning for the future (e.g., facilitates involvement of patient and caregivers in planning medical, educational, and psychosocial interventions to suit their needs; identifies a time when the patient can still participate in medical, legal, and financial decisions; and make proxy plans); 4) appropriate access to services (e.g., patients and families can take advantage of appropriate programs and services, including community-based resources); and 5) risk reduction (e.g., greater attention to detail to prevent delirium, motor vehicle accidents, medication errors, and financial difficulties).

Clinical Importance of Changes in Outcome Measures

The inconsistent reporting of a constellation of important patient (and caregiver) outcomes limits the clinical interpretation of the changes in individual outcomes on the overall patient (and caregiver) health and well-being. For example, small improvement in global cognitive function in the absence of improvement in physical functioning (e.g., ADLs) and HRQL is less convincing of true benefit compared with small improvement in cognitive function accompanied by improvements in ADLs or HRQL, and certainly delay in institutionalization. FDA-approved medications for AD, including donepezil, galantamine, rivastigmine, and memantine, clearly can

improve measures of global cognitive outcomes in people with mild to moderate dementia in the short-term (mainly 6 months). In addition, donepezil, galantamine, and rivastigmine can improve measures of global functioning. The average effects range from 1- to 3-point change on the ADAS-cog and a fraction of a point on the CIBIC-plus. The clinical interpretation of these changes is subjective, and not widely agreed upon. We framed our results based on the precedent used by ACP and AAFP, however, such that a change of 4 points or more on the ADAS-cog over 6 months or any change on the CIBIC-plus is clinically meaningful.[94] Based on these thresholds, we interpret our review findings to show small but likely clinically unimportant differences in cognitive outcomes, and small but unclear benefit in global functioning (because this outcome was less consistently reported, and the magnitude of change was <1 point). An analogous example is the interpretation of change on a better known clinically relevant scale, such as instruments measuring ADLs. Although any change in ADLs is clinically significant, the clinical meaning of a fraction of a point or a portion of an ADL is less clear. Because these changes in scores represent an average effect across a population, one could argue that a clinically more intuitive way of understanding the benefit is the reporting of dichotomous outcomes, such as the proportion of people with a clinically significant change on the ADAS-cog in the treatment group versus the placebo group. For example, it would be helpful to know if the average effect of a 2-point change on the ADAS-cog represents 50 percent of participants with a 4-point improvement (i.e., 50% "responders") or 100 percent of participants with a 2-point improvement (i.e., 100% "nonresponders"). These dichotomous outcomes were rarely reported.

Complex caregiver interventions resulted in improvement in caregiver burden and depression outcomes. We found no guidance on the interpretation of clinically meaningful changes on caregiver burden and depression outcome measures. In general, absolute changes ranged from 0 to 5 points on multiple-item instruments (88-point Zarit CBI, 96-point RMBPC subscale, and 60-point CES-D). For depression outcomes, control groups typically showed small increases in depressed mood and intervention groups showed small improvements; however, baseline depression was typically in the minimal or mild range (e.g., average score of 12–15 on the CES-D, in which a score of 16 indicates possible depression). Using accepted thresholds to interpret standardized effect sizes, the effects on caregiver burden and depression outcomes ranged from very small (0.1) to small (0.4).

The clinical meaning of the changes is further complicated by the inconsistent reporting of other important and related outcome measures, such as HRQL or institutionalization. Many trials, because of their relatively short duration, were not designed to evaluate the impact of interventions on institutionalization. Institutionalization was rarely reported, and when reported, showed no statistically significant difference between treatment and control groups. Delay of institutionalization is clearly a clinically important outcome, as well as one of the main factors in cost of care and cost-effectiveness of interventions.

Availability of Nonpharmacologic Interventions

The most promising nonpharmacologic interventions for people with mild to moderate dementia are complex caregiver interventions, which often involve multiple components (e.g., individual support, case management), as well as cognitive stimulation. Neither type of intervention is widely available in the United States. In fact, many trials evaluating complex caregiver

interventions used widely available resources, such as support groups provided by (or modeled after) the Alzheimer's Association, as the control arm. From our review, the optimal intervention components for effective interventions (caregiver interventions) and the optimal format or intensity (dose/duration) are unclear, but as a whole, both caregiver and cognitive stimulation interventions can be quite resource-intensive, requiring specialist staff with training and multiple sessions over several months.

Review Limitations

Our review has several important limitations given our primary aim and targeted audience—the USPSTF. Our review is not meant to be a comprehensive review of all cognitive screening instruments, nor a comprehensive review of all dementia treatments/interventions. We focused on the best-quality evidence of estimates of diagnostic accuracy of cognitive screening instruments in unselected community-dwelling older adults relevant to primary care in the United States. We therefore excluded case-control studies, studies without a true reference standard, studies only evaluating the correlation between screening instruments, instruments with lengthy administration time, institutionalized older adults, and populations selected for cognitive impairment or referred for subjective memory complaints, including populations exclusively from memory, neurology, and geriatric psychiatry clinics, and Alzheimer's Disease Research Centers. Due to these restrictions in scope, our review does not address several important aspects of screening test performance, including: the psychometric properties of testing, validation of screening instruments in different languages, optimal cut-points in scoring the included instruments, differential ability of instruments to detect different types of dementia, comparative performance of screening instruments, or ability to improve diagnostic performance by combining screening instruments (unless the instrument itself is a combination of instruments, such as the Mini-Cog is a combination of the CDT plus three-item recall).

Likewise, our review focuses on the best-quality evidence for specific currently used interventions aimed at community-dwelling older adults with screen-detected cognitive impairment, specifically people with mild to moderate dementia or MCI. Therefore, we excluded experimental interventions, interventions aimed at later stages of dementia, interventions aimed primarily at symptom management, institutionalized populations, and populations with moderately severe to severe dementia. We also excluded primary prevention trials; that is, trials in healthy older adults evaluating interventions to prevent, delay, or slow cognitive decline. Despite our best efforts, there may have been some inconsistency in operationalizing these inclusion criteria due to reporting in individual studies, studies with mixed populations, and different definitions of care settings in different countries (i.e., we included people in assisted living facilities, older adult homes, and residential care facilities, but excluded people in skilled nursing homes). For evidence of effectiveness, we limited our included studies to trial designs with a true or usual care control. Again, due to limited reporting of usual care and control groups in individual trials, there may have been some inconsistency in the operationalization of usual care or minimally active control group. Due to these limitations, our review does not address: the overall effectiveness (or harms) of each type of intervention, only the effectiveness (or harms) in a subset of people with mild to moderate dementia or MCI, the comparative effectiveness of different types of interventions (what works better or what dose works better), or the minimal/necessary components (including intensity/duration) needed for the effectiveness of

complex interventions.

Due to resource limitations, we did not search FDA databases or contact industry for data on pharmacologic interventions. However, an older review from 2006 by Hansen and colleagues designed to evaluate the effectiveness and comparative effectiveness of AChEIs and memantine included a hand search for unpublished research submitted to the FDA and dossiers submitted by pharmaceutical companies, which did not contribute any unpublished evidence on harms for currently used medications (excluding tacrine).[418] Due to resource limitations, we focused our synthesis of adverse effects on those interventions with a benefit, serious harms, larger observational studies (n>1,000), or those observational studies with longer-term followup (>1 year).

Study Limitations and Future Research Needs

Despite such a large and rapidly growing body of research around screening for cognitive impairment, as well as treatment and management of people with dementia and MCI (**Appendix G Table 1**), there are several important research gaps. First is the lack of evidence around decisionmaking outcomes. Experts in the field argue that early diagnosis is important because it impacts clinical and patient decisionmaking. While this is a logical argument, there is currently little to no empirical evidence to support it. Older adults with dementia generally have multiple comorbid conditions in addition to their cognitive impairment. Researchers should conduct screening trials or observational studies to demonstrate changes in decisionmaking (at a minimum) and patient or caregiver outcomes (as an ideal). Studies examining how (and if) earlier identification of cognitive impairment or earlier management of patients with dementia and their caregivers impact clinician decisionmaking (e.g., medical management of comorbid conditions) and patient and family decisionmaking (e.g., advanced planning) are extremely important aspects to understand in order to better manage this rapidly growing health care problem.

Second, and perhaps equally as important, is how best to identify persons with cognitive impairment. Dementia is underdiagnosed in primary care. Researchers should conduct studies to understand how best to (systematically) identify persons with cognitive impairment. Based on empiric evidence, it is still unclear how best to apply brief cognitive assessment tools to aid in the identification of dementia. These brief instruments can be applied broadly to all older adults, (i.e., population-based screening) or in more targeted approaches, as suggested by the Annual Wellness Visit. To assist operationalizing the Annual Wellness Visit's mandate to assess for cognitive impairment, experts have suggested a step-wise approach to identify persons in whom a brief cognitive instrument should be applied. Research comparing what criteria (e.g., age, comorbid condition, functional status) should lead primary care clinicians to conduct cognitive assessment is needed.

Third, the harms of screening are very poorly studied. Some have argued that the harms of screening, other than the opportunity cost, are minimal given the noninvasive nature of screening and subsequent diagnostic workup. Other experts have argued that the harms of screening and mislabeling persons with dementia are quite real given the variation in practice of diagnostic confirmation of disease. If a broader adoption of screening for cognitive impairment is

implemented in primary care, we need a better understanding of what, or if, harmful tradeoffs exist.

Fourth, while there are many well-designed diagnostic accuracy studies, there is still very little reproducibility of test performance of brief instruments that could be used in primary care among these studies. In some cases in which there are multiple studies, there appears to be important variation in test performance, which may be due to differences in populations or administration and scoring (choice of cut-point) of the instrument itself. Additional evaluation of these screening instruments in more representative populations is needed after studies have been validated in higher-risk populations (e.g., memory clinics) and/or with initial validation studies (e.g., case-control studies). Well-conducted diagnostic accuracy studies for the most promising instruments need to be reproduced in relevant populations. These diagnostic accuracy studies should report adequate baseline population characteristics, including age and education (any characteristic known to affect normative values of the instrument). These studies should report multiple cut-points if applicable, and be explicit about scoring methods or choice of cut-points (if multiple options exist).

Fifth, the clinical areas of defining, diagnosing, and treating cognitive impairment earlier (before loss of IADLs) are rapidly evolving. Experts in this field are actively working to refine diagnostic criteria and to standardize the identification of people with MCI or "mild neurocognitive disorder," as called in the DSM-V. Ongoing research studies are evaluating different variants and operational definitions of the current MCI criteria. Future research should focus on improved criteria and subtypes of MCI with demonstrated prognostic and predictive value. The outcome (i.e., progression, regression, stability) of MCI reflects: 1) its underlying etiology, and thus subtypes should map to the underlying disease (e.g., amnestic MCI is more likely to represent underlying AD and therefore more likely to progress to dementia than nonamnestic MCI); 2) the individual patient's characteristics (i.e., age and comorbid conditions); and 3) how the population being studied is selected (e.g., clinic, research setting, community setting). These considerations should be incorporated into future research to understand the natural history of MCI, develop or improve MCI diagnostic criteria, identify subtypes, and standardize criteria. Criteria with established predictive value should then be operationalized in a standardized fashion in research studies, both in specialized settings (e.g., Alzheimer's Disease Research Center, memory clinics) and less selected populations (e.g., primary care or community-based settings).

Sixth, similar to diagnostic accuracy studies for detecting dementia, diagnostic accuracy studies for MCI should also report adequate baseline population characteristics and be explicit about scoring/cut-points (thresholds) used, reporting test performance for multiple cut-points if applicable (e.g., for different levels of age and education).

Seventh, while our report did not evaluate the role of biomarkers (i.e., plasma, urine, CSF) or imaging in screening for diseases affecting cognition, such as AD (as this field is still developmental), it is an active field of research. Ongoing research focuses on using these tests for early (even preclinical) detection of disease. If these types of tests prove useful in the diagnosis of types of dementia or MCI, they may provide an additional "gold standard" for diagnostic accuracy and calibration. They may also be useful for case-finding or screening

purposes, should the eventual discovery of reliable, valid, sensitive, specific, and affordable tests manifest.

Eighth, the body of evidence around mild to moderate dementia treatment and MCI is very large and rapidly evolving (**Appendix G Table 1**). The overwhelming majority of evidence is in people with AD, and additional research is needed for the effectiveness of various interventions in other types of dementia, including VaD, FTD, and DLB.

Ninth, the average treatment effects reported for FDA-approved medications for AD and intensive interventions are disappointingly small. Consequently, it is difficult to interpret the clinical importance of such small changes. It is also possible that outcome measures themselves may have limited responsiveness (sensitivity to detect change) in patients with less pronounced cognitive impairment. For example, the ADAS-cog and MMSE may have ceiling effects and are therefore unable to show benefit in people with MCI or even mild dementia. Other important outcomes, such as global functioning, HRQL, global physical functioning, emergent or unexpected health care utilization, and institutionalization, are inconsistently reported (with the exception of CIBIC-plus as reported in drug trial literature). Inconsistent reporting could be symptomatic of selective reporting or inconsistent use of these outcome measures. Whatever the reason, this limits our ability to interpret effects on these outcomes as a body of literature. Given these challenges in interpreting the clinical significance of benefit (or even lack of benefit) in treatment trials, we suggest that trials should consistently report a constellation of important self-reported and objective outcomes (e.g., emergency visits and institutionalization). This might be difficult given that trials are costly to conduct and have very limited duration of followup, in most cases, generally less than 12 months (many drug trials have only 6 months followup). Longer duration of trials is also important to understanding the clinical significance of small changes on outcome measures, especially during earlier stages of dementia (i.e., may need longer duration of followup to observe benefit). For outcome measures with accepted thresholds of clinical significance, consistent and standardized (using same thresholds) reporting of results that is dichotomized into “responders” and “nonresponders” will also be helpful in interpreting the small average effects on continuous outcome measures.

Finally, while our report did not evaluate the effectiveness of experimental therapies targeted to alter the disease process, disease-modifying therapies (e.g., immunotherapy) to slow cognitive decline is an extremely active area of research.

Conclusions

Currently, there is no trial evidence that addresses whether screening for cognitive impairment or early diagnosis of cognitive impairment improves patient, caregiver/family, or clinician decisionmaking or improves important patient, caregiver, or societal outcomes. Several brief screening instruments can adequately detect dementia, especially in populations with a higher prevalence of underlying dementia. Harms of screening for cognitive impairment, however, are not well studied. AChEIs, memantine, complex caregiver interventions, and cognitive stimulation all have evidence to support their use in mild to moderate dementia. However, the average effects of benefits observed in trials for these medications and caregiver interventions are generally small and in people with moderate (as opposed to mild) dementia. Therefore, the

clinical importance and applicability of these interventions to screen-detected people with cognitive impairment is not clear. This benefit is also limited by commonly experienced side effects of AChEIs and limited availability of complex caregiver interventions. Cognitive stimulation appears promising in people with MCI and mild dementia, but the evidence base is small and the imprecision around the estimates of benefit limit the clinical interpretation of the benefit on cognitive functioning. Current evidence on screening for MCI includes studies that use different criteria to define this entity, sensitivity of the few instruments evaluated to detect MCI are lower (than sensitivity to detect dementia), despite choice of diagnostic cut-point, and there is little evidence for any pharmacologic or nonpharmacologic interventions to improve or preserve patient functioning in people with MCI.

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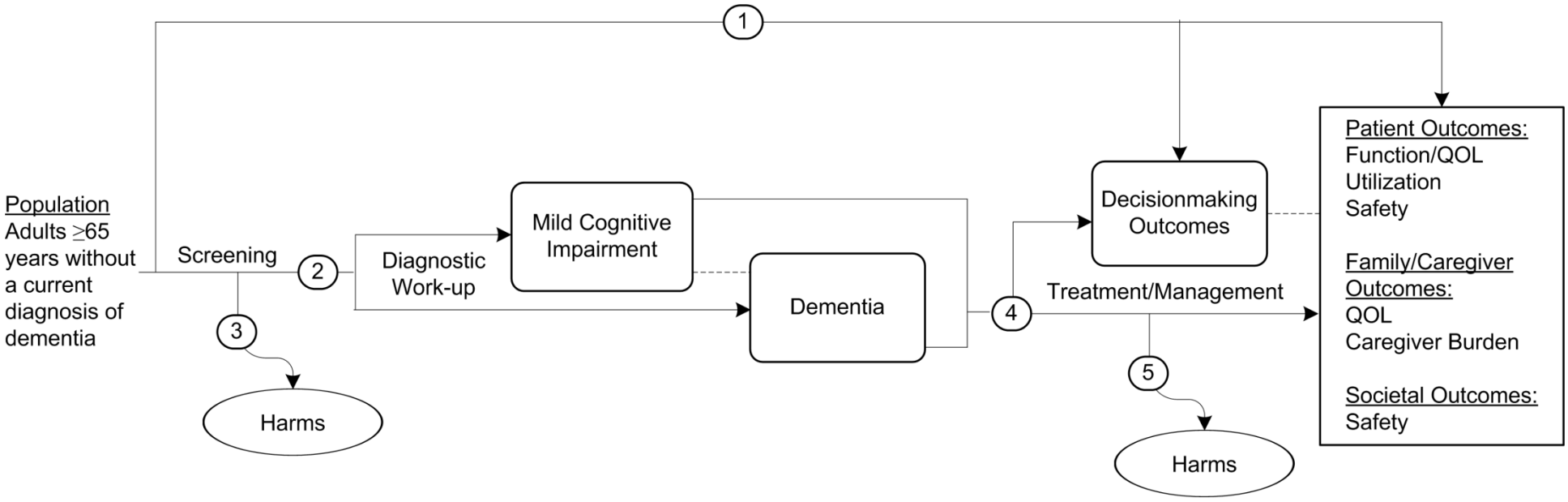
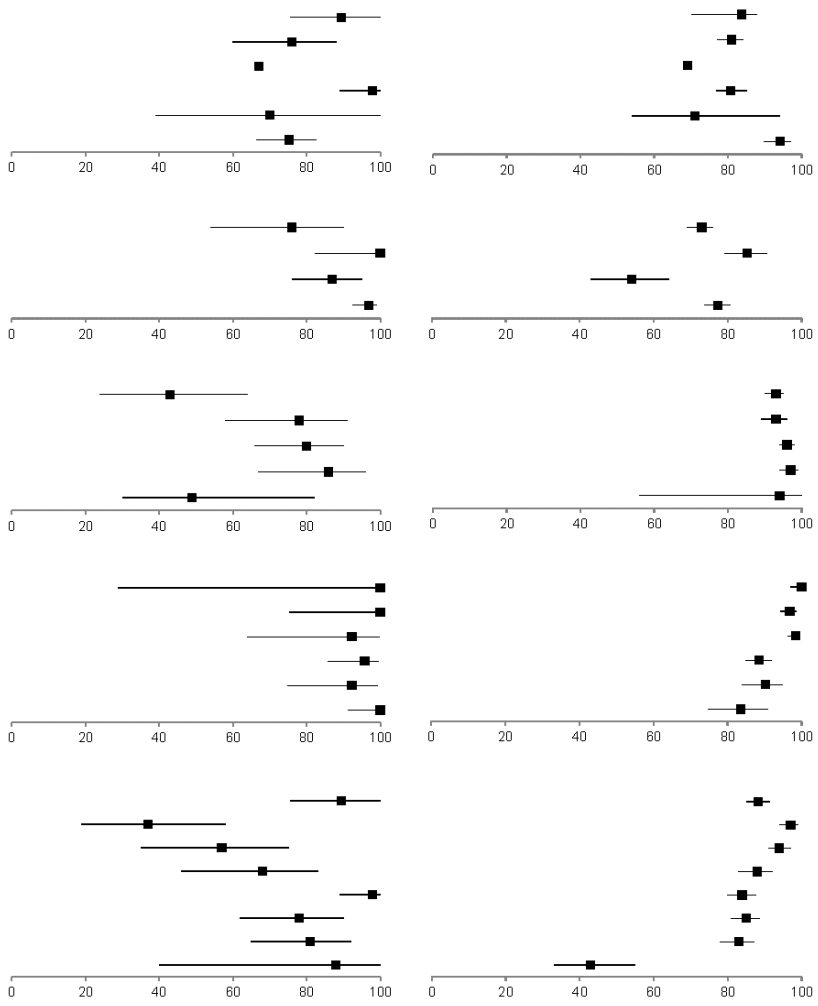
Figure 1. Analytic Framework



Abbreviation: QOL = quality of life.

Figure 2. Diagnostic Accuracy of Very Brief Screening Instruments for Dementia (Key Question 2)

Study	n	Prevalence	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
CDT							
Fuchs 2011	423	5.0	NR	89.5 (75.7, 100.0)	83.7 (80.1, 87.3)		
Kirby 2001	648	6.3	<6	76 (60, 88*)	81 (77, 84*)		
Ball 2001	53	9.0	NR	67 (NR††)	69 (NR††)		
Del Ser 2006	416	11.5	NR	97.9 (88.9, 99.9**)	80.7 (76.3, 84.6**)		
Grober 2008	318	17.6	13	70 (39, 100)	71 (54, 94)		
Wolf-Klein 1989	312	47.1	NR	75.2* (66.5, 82.6*)	94.2* (89.9, 97.1*)		
Mini-cog							
Holsinger 2012	630	3.3	2/3	76 (54, 90)	73 (69, 76)		
Fuchs 2011	423	5.0	NR	100.0 (82.4, 100.0)	85.2 (81.4, 88.4)		
Kaufer 2008	146	38.0	0	87 (76, 95)	54 (43, 64)		
Borson 2006	371	40.2	2/3	96.8* (92.6, 98.9*)	77.4* (71.3, 82.8*)		
MIS/MIS-T							
Holsinger 2012	630	3.3	4/5	43 (24, 64)	93 (90, 95)		
Lipton 2003 (T)	300	9.0	4	78 (58, 91**)	93 (89, 96**)		
Buschke 1999	483	10.4	4	80 (66, 90**)	96 (94, 98**)		
Kuslansky 2002	240	11.7	NR	86 (67, 96**)	97 (94, 99**)		
Grober 2008	318	17.6	4	49 (30, 82)	94 (56, 100)		
SPMSQ/MSQ							
Erkinjuntti 1987 (S)	119	2.5	7/8	100 (29, 100**)	100 (97, 100**)		
Hooijer 1992 (S)	358	3.6	7/8	100 (75.3, 100**)	96.8 (94.4, 98.4**)		
Hooijer 1992 (M)	358	3.6	7/8	92.3 (64.0, 99.8**)	98.3 (96.3, 99.4**)		
Del Ser 2006 (S)	416	11.5	NR	95.8 (85.8, 99.5**)	88.5 (84.9, 91.7**)		
Fillenbaum 1990 (S)	164	16.4	NR	92.3* (74.9, 99.1*)	90.2* (83.9, 94.7*)		
Fillenbaum 1990 (M)	164	16.4	7/8	100* (86.8, 100*)	83.5* (76.0, 89.3*)		
Verbal Fluency							
Fuchs 2011	423	5.0	NR	89.5 (75.7, 100.0)	88.3 (85.1, 91.4)		
Lipton 2003	300	9.0	13.0	37 (19, 58**)	97 (94, 99**)		
Lipton 2003	300	9.0	15.0	57 (35, 75**)	94 (91, 97**)		
Lipton 2003	300	9.0	19.0	68 (46, 83**)	88 (83, 92**)		
Del Ser 2006	416	11.5	NR	97.9 (88.9, 100**)	83.9 (79.8, 87.6**)		
Heun 1998	287	12.9	≤14	78 (62, 90**)	85 (80, 89**)		
Heun 1998	287	12.9	≤14	81 (65, 92**)	83 (78, 87**)		
Grober 2008	318	17.6	14	88 (40, 100)	43 (33, 55)		



* Calculated from 2x2 table

†† Confidence intervals could not be calculated

** Calculated using the sensitivity, specificity, and prevalence of cognitive impairment

Abbreviations: CDT – Clock Drawing Test; CI – Confidence interval; M – MSQ; MIS - Memory Impairment Screen; MIS-T – Memory Impairment Screen by Telephone; MSQ – Mental Status Questionnaire; NR – Not reported; S – SPMSQ; SPMSQ – Short Portable Mental Status Questionnaire; T – MIS-T

Figure 3. Diagnostic Accuracy of Brief Screening Instruments for Dementia (Key Question 2)

Study	n	Prevalence	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)
AMT					
Hooijer 1992	358	3.6	7/8	92.3 (64.0, 99.8**)	95.4 (92.6, 97.3**)
Rait 2000	96	6.0	8/9	100 (54, 100)	83 (76, 91)
Rait 2000 (Gujarati)	62	11.0	6	100 (16.0, 100)	95.0 (85.8, 99.0)
Rait 2000 (Pakistani)	39	11.0	7	100 (66.4, 100)	86.7 (68.4, 95.6)
Brodaty 2002	269	29.0	7/8	42 (31, 53**)	93 (89, 96**)
FCSRT					
Del Ser 2006	416	11.5	NR	100 (92.6, 100**)	87.2 (83.4, 90.5**)
Grober 2008	318	17.6	25	86 (41, 100)	73 (56, 96)
7MS					
Solomon 2000	137	8.0	0.3/0.7	100† (71.5, 100†)	100† (86.8, 100†)
Del Ser 2006	416	11.5	NR	100 (92.6, 100**)	95.1 (92.4, 97.1**)
TICS					
Lipton 2003	300	9.0	28	74 (54, 89**)	86 (81, 90**)
Manly 2011	377	14.1	22/23	88 (77, 96**)	87 (83, 91**)

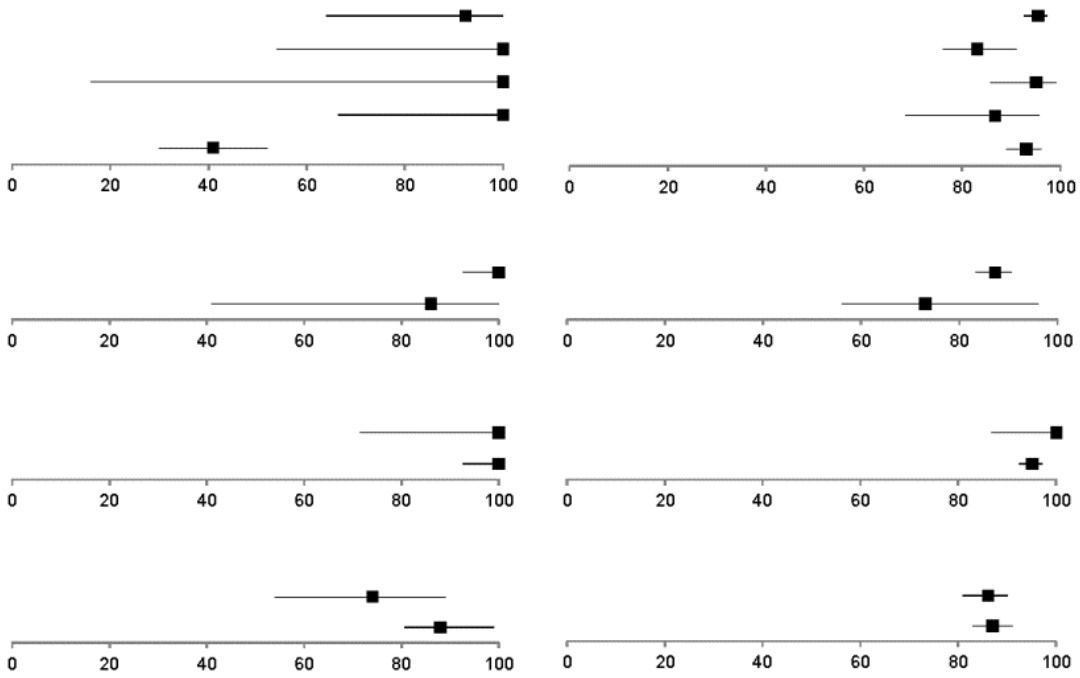
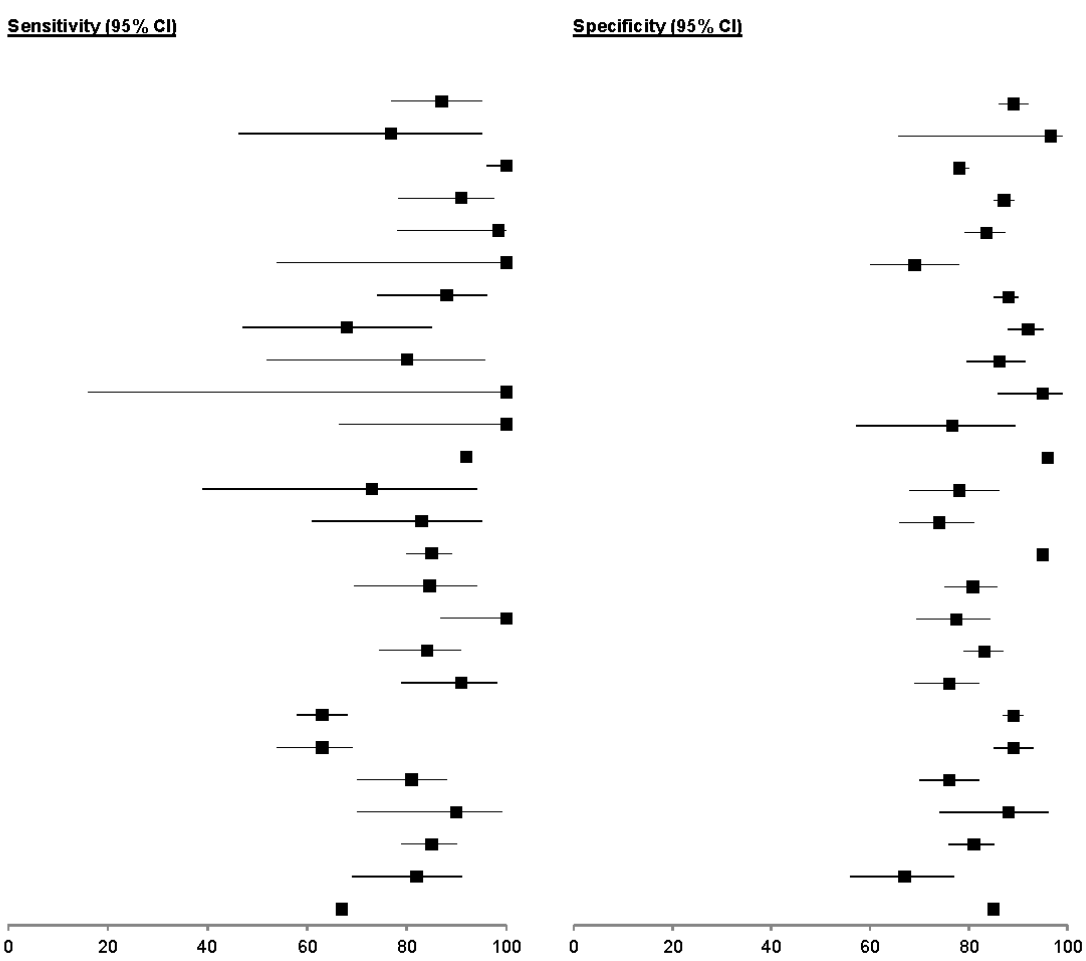


Figure 3. Diagnostic Accuracy of Brief Screening Instruments for Dementia (Key Question 2)

Study	n	Prevalence	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)
MMSE					
Fong 2011	709	1.2	23/24	87 (78, 95)	89 (86, 92)
Hooijer 1992	358	3.6	23/24	76.9 (46.2, 95.0**)	96.5 (94.0, 98.2**)
Gagnon 1990	2730	3.7	24	100 (96, 100*)	78 (77, 80*)
Cullen 2005	1115	3.9	23/24	90.9 (78.3, 97.5**)	87.1 (85.0, 89.1**)
Callahan 2002	269	4.3	24/25	98.4 (78.2, 100**)	83.6 (79.1, 87.4**)
Rait 2000	96	6.0	26/27	100 (54, 100)	69 (60, 78)
Kirby 2001	648	6.3	23/24	88 (74, 96*)	88 (85, 90*)
Cruz-Orduna 2011	160	9.4	18/19	80.0 (51.9, 95.7**)	86.2 (79.5, 91.4**)
Lavery 2007	339	9.7	21/22	68 (47, 85**)	92 (88, 95**)
Rait 2000 (Gujarati)	62	11.0	24	100 (16.0, 100)	95.0 (85.8, 99.0)
Rait 2000 (Pakistani)	39	11.0	27	100 (66.4, 100)	76.7 (57.3, 89.4)
Heun 1998	287	12.9	23/24	92 (78, 98**)	96 (93, 98**)
Morales 1997 (urban)	97	13.2	21	73 (39, 94**)	78 (68, 86**)
Morales 1997 (rural)	160	13.2	20	83 (61, 95**)	74 (66, 81**)
Grut 1993	668	14.1	24/25	85* (80, 89*)	95* (94, 96*)
Kay 1985	274	14.2	24/25	84.6 (69.5, 94.1**)	80.8 (75.2, 85.7**)
Fillenbaum 1990	164	16.4	NR	100* (86.8, 100*)	77.4* (69.4, 84.2*)
Reischies 1997	449	19.4	24/25	84.1 (74.5, 90.9**)	83.1 (78.9, 86.9**)
Jeong 2004	235	19.6	18/19	91 (79, 98)	76 (69, 82)
McDowell 1997	1600	23.0	24	63 (58, 68**)	89 (87, 91**)
Waite 1998	360	27.5	23/24	84 (75, 90**)	88 (84, 92**)
Brodaty 2002	283	29.0	24/25	81 (70, 88**)	76 (70, 82**)
Scharre 2010	63	33.0	26/27	90 (70, 99**)	88 (74, 96**)
Kahle-Wrobleski	435	36.0	24	85** (79, 90**)	81** (76, 85**)
Kaufer 2008	146	38.0	26/27	82 (69, 91)	67 (56, 77)
Jorm 1996	143	NR	26/27	67 (NR††)	85 (NR††)



* Calculated from 2x2 table

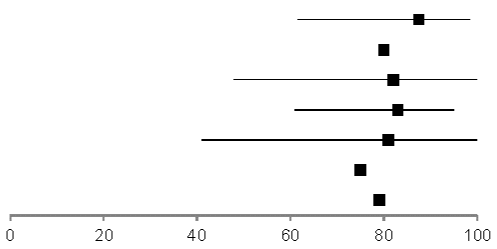
†† Confidence intervals could not be calculated

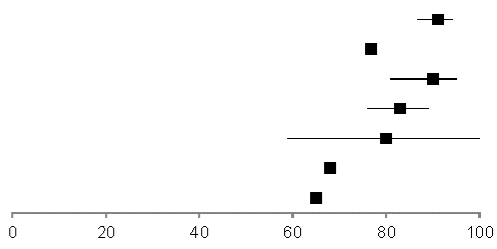
** Calculated using the sensitivity, specificity, and prevalence of cognitive impairment

Abbreviations: AMT – Abbreviated Mental Test ; CI – Confidence interval; FCSRT – Free and Cued Selective Reminding Test; 7MS – 7 Minute Screen; TICS – Telephone for Cognitive Status; MMSE – Mini-Mental State Examination; NR – Not reported

Figure 4. Diagnostic Accuracy of Self-Administered Screening Instruments for Dementia (Key Question 2)

Study	n	Prevalence	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)
IQCODE					
Tokuhara 2006 (F)	230	7.0	3.5	87.5 (61.7, 98.5**)	91.1 (86.8, 94.3**)
Cruz-Orduna 2011 (F)	160	9.4	3.65/3.69	80.00 (51.91, 95.67**)	76.71 (68.80, 83.18**)
Morales 1997 (F) (urban)	97	13.2	3.27	82 (48, 98**)	90 (81, 95**)
Morales 1997 (F) (rural)	160	13.2	3.31	83 (61, 95**)	83 (76, 89**)
Grober 2008 (S)	318	17.6	3.3	81 (41, 100)	80 (59, 100)
Jorm 1996 (S)	143	NR	3.31/3.38	75 (NR††)	68 (NR††)
Jorm 1996 (F)	143	NR	3.27/3.30	79 (NR††)	65 (NR††)





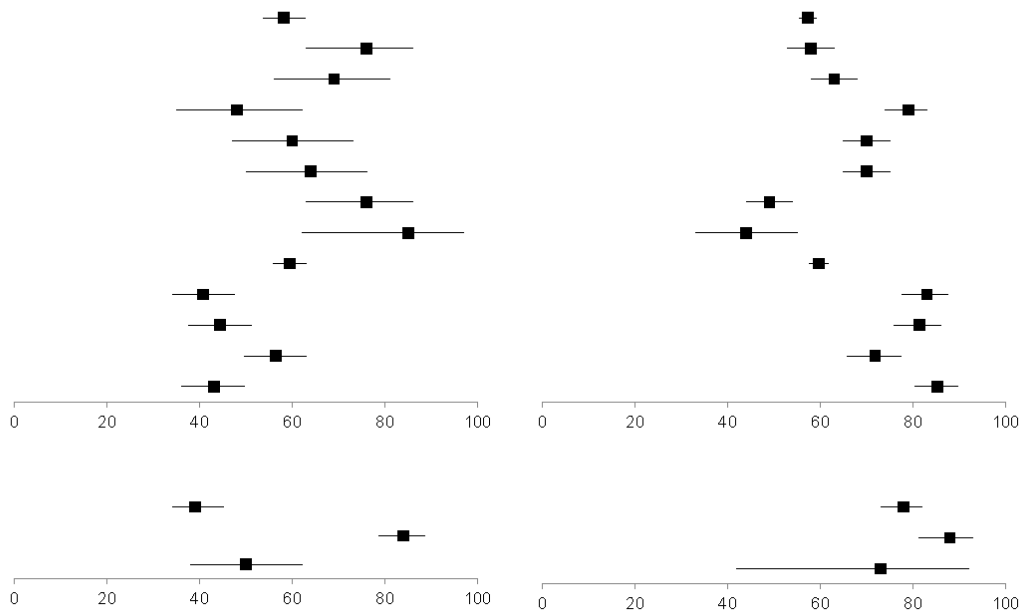
†† Confidence intervals could not be calculated

** Calculated using the sensitivity, specificity, and prevalence of cognitive impairment

Abbreviations: CI – Confidence interval; F– Full IQCODE; IQCODE – Informant Questionnaire on Cognitive Decline in the Elderly; NR – Not reported; S – Short IQCODE

Figure 5. Diagnostic Accuracy of Very Brief Screening Instruments for MCI (Key Question 2)

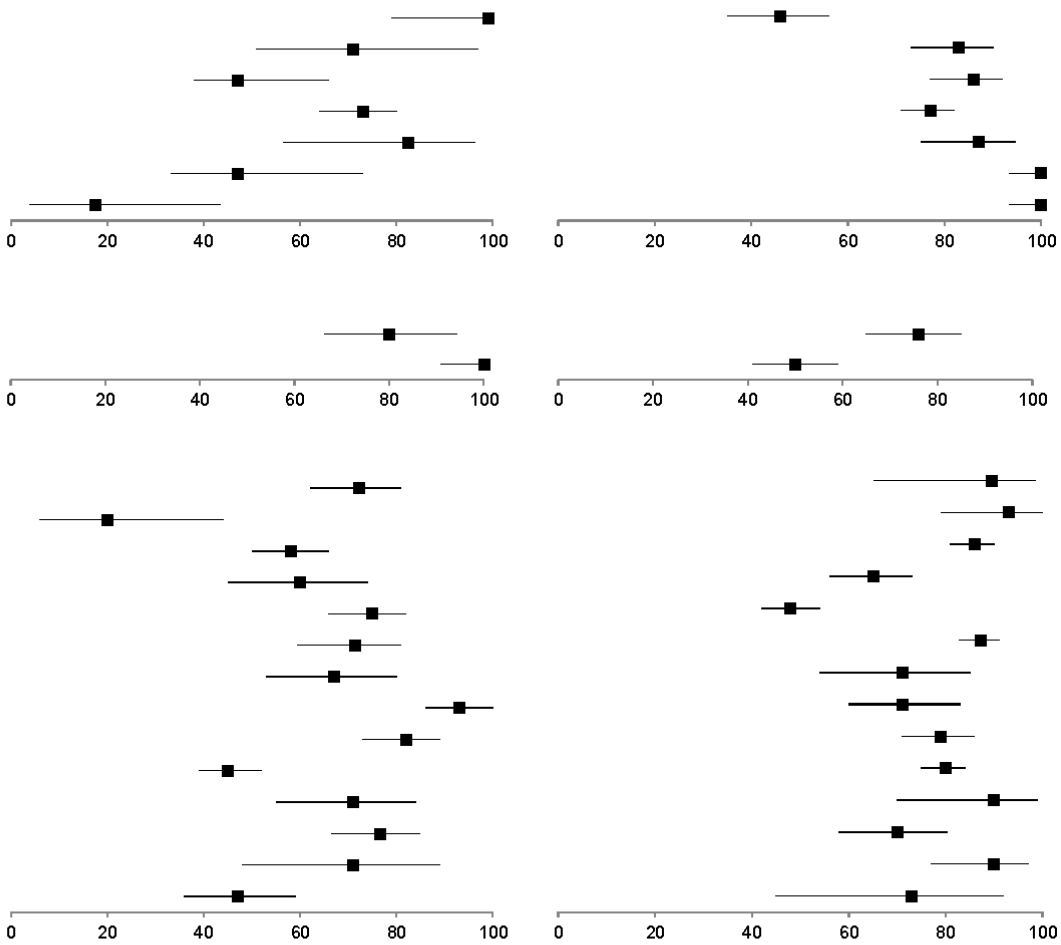
Study	n	Prevalence	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)
CDT					
Ehreke 2009 (original)	3198	15.0‡‡	9	58.2 (53.7, 62.7**)	57.3 (55.4, 59.2**)
Ehreke 2011 (Shulman)	428	13.6‡‡	1/2	76 (63, 86**)	58 (53, 63**)
Ehreke 2011 (Ihl)	428	13.6‡‡	9/10	69 (56, 81**)	63 (58, 68**)
Ehreke 2011 (Rouleau)	428	13.6‡‡	7/8	48 (35, 62**)	79 (74, 83**)
Ehreke 2011 (Babins)	428	13.6‡‡	15/16	60 (47, 73**)	70 (65, 75**)
Ehreke 2011 (Mendez)	428	13.6‡‡	18/19	64 (50, 76**)	70 (65, 75**)
Ehreke 2011 (Lin)	428	13.6‡‡	2/3	76 (63, 86**)	49 (44, 54**)
Donnelly 2008	100	20.0‡‡	1 SD	85 (62, 97)	44 (33, 55)
Ehreke 2009 (modified)	3198	24.6‡‡	9	59.4 (55.9, 62.9**)	59.7 (57.7, 61.7**)
Lee 2008 (Freedman)	465	48.2‡‡	9/10	40.7 (34.1, 47.4**)	83.0 (77.6, 87.5**)
Lee 2008 (Todd)	465	48.2‡‡	6/6.5	44.4 (37.6, 51.0**)	81.3 (75.8, 86.0**)
Lee 2008 (Rouleau)	465	48.2‡‡	7/8	56.4 (49.5, 62.9**)	71.8 (65.7, 77.4**)
Lee 2008 (CERAD)	465	48.2‡‡	1/2	43.0 (36.3, 49.6**)	85.3 (80.4, 89.7**)
Mini-cog					
Holsinger 2012	630	12.1	2/3	39 (34, 45)	78 (73, 82)
Borson 2006	371	39.2	2/3	84* (78.6, 88.5*)	87.9* (81.3, 92.8*)
Kaufer 2008	91	83.5‡‡	0	50 (38, 62)	73 (42, 92)



‡‡ Prevalence for MCI only (no demented patients included in the sample and/or analysis)

Figure 6. Diagnostic Accuracy of Brief Screening Instruments for MCI (Key Question 2)

Study	n	Prevalence	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)
TICS-M					
Vercambre 2010	120	15.0	27	99 (88, 100**)	46 (35, 56**)
Vercambre 2010	120	15.0	31	71 (51, 87**)	83 (73, 90**)
Vercambre 2010	120	15.0	34	47 (28, 66**)	86 (77, 92**)
Manly 2011	377	18.0	26/27	73 (64, 80**)	77 (71, 82**)
Cook 2009	71	23.9‡‡	34	82.4 (56.6, 96.2**)	87.0 (75.1, 94.6**)
Cook 2009	71	23.9‡‡	31	47.1 (23.0, 72.2**)	100 (93.4, 100**)
Cook 2009	71	23.9‡‡	26	17.6 (3.8, 43.4**)	100 (93.4, 100**)
MOCA					
Markwick 2012	99	20.2‡‡	25/26	80.0* (56.3, 94.3*)	76.0* (65.0, 84.9*)
Lee 2008	152	24.3‡‡	25/26	100 (91, 100**)	50 (41, 59**)
MMSE					
Cullen 2005	1115	8.7	23/24	72.2 (62.1, 80.8**)	89.4 (65.3, 98.6**)
Donnelly 2008	100	20.0‡‡	1 SD	20 (6, 44)	93 (84, 97)
Rideaux 2012 (White)	509	28.7‡‡	25/26	58 (50, 66**)	86 (81, 90**)
Tariq 2006 (<HS)	187	29.0‡‡	28.5	60 (45, 74**)	65 (56, 73**)
Tariq 2006 (≥HS)	433	29.0‡‡	29.5	75 (66, 82**)	48 (42, 54**)
Callahan 2002	269	30.7	25/26	71.5 (59.5, 80.9**)	87.3 (82.7, 91.1**)
Rideaux 2012 (Black)	124	39.4‡‡	22/23	67 (53, 80**)	71 (54, 85**)
Rideaux 2012 (Latino)	68	39.7‡‡	24/25	93 (86, 100)	71 (60, 83)
Jeong 2004	235	42.6	20/21	82 (73, 89)	79 (71, 86)
Saxton 2009	524	43.5‡‡	28	45 (39, 52**)	80 (75, 84**)
Scharre 2010	42	50.0‡‡	NR	71 (55, 84**)	90 (70, 99**)
Cruz-Orduna 2011	160	56.3	23/24	76.67 (66.57, 84.94**)	70.0 (57.87, 80.38**)
Scharre 2010	63	66.0	27/28	71 (48, 89**)	90 (77, 97**)
Kaufer 2008	91	83.5‡‡	27/28	47 (36, 59)	73 (45, 92)



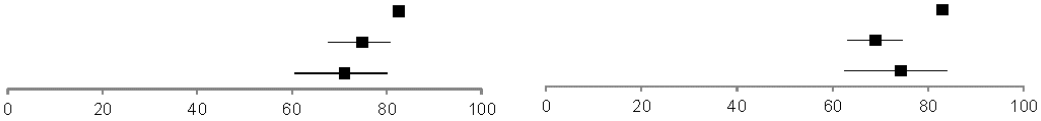
‡‡ Prevalence for MCI only (no demented patients included in the sample and/or analysis)

** Calculated using the sensitivity, specificity, and prevalence of cognitive impairment

Abbreviations: CI – Confidence interval; HS – High school; TICS – Modified Telephone for Cognitive Status; MMSE – Mini-Mental State Examination; NR – Not reported

Figure 7. Diagnostic Accuracy of Self-Administered Screening Instruments for MCI (Key Question 2)

Study	n	Prevalence	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)
IQCODE					
Tokuhara 2006 (F)	230	17.0	3.3	82.6 (NR††)	83.0 (NR††)
Ayalon 2011 (S)	441	42.0‡‡	>3	74.8 (67.7, 80.7**)	69.0 (63.1, 74.7**)
Cruz-Orduna 2011 (F)	160	56.3	3.31/3.35	71.11 (60.60, 80.18**)	74.29 (62.44, 83.99**)



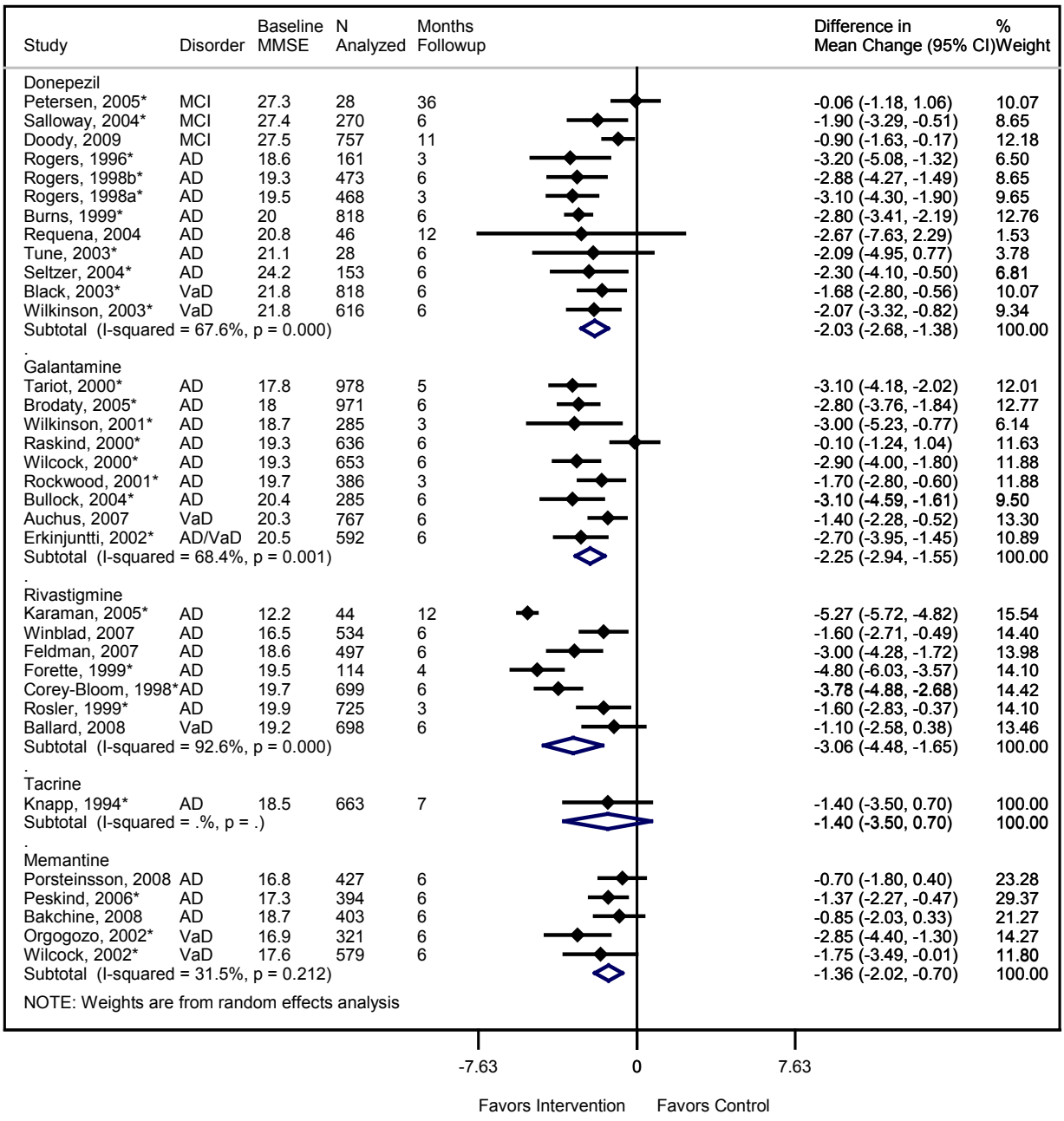
‡‡ Prevalence for MCI only (no demented patients included in the sample and/or analysis)

†† Confidence intervals could not be calculated

** Calculated using the sensitivity, specificity, and prevalence of cognitive impairment

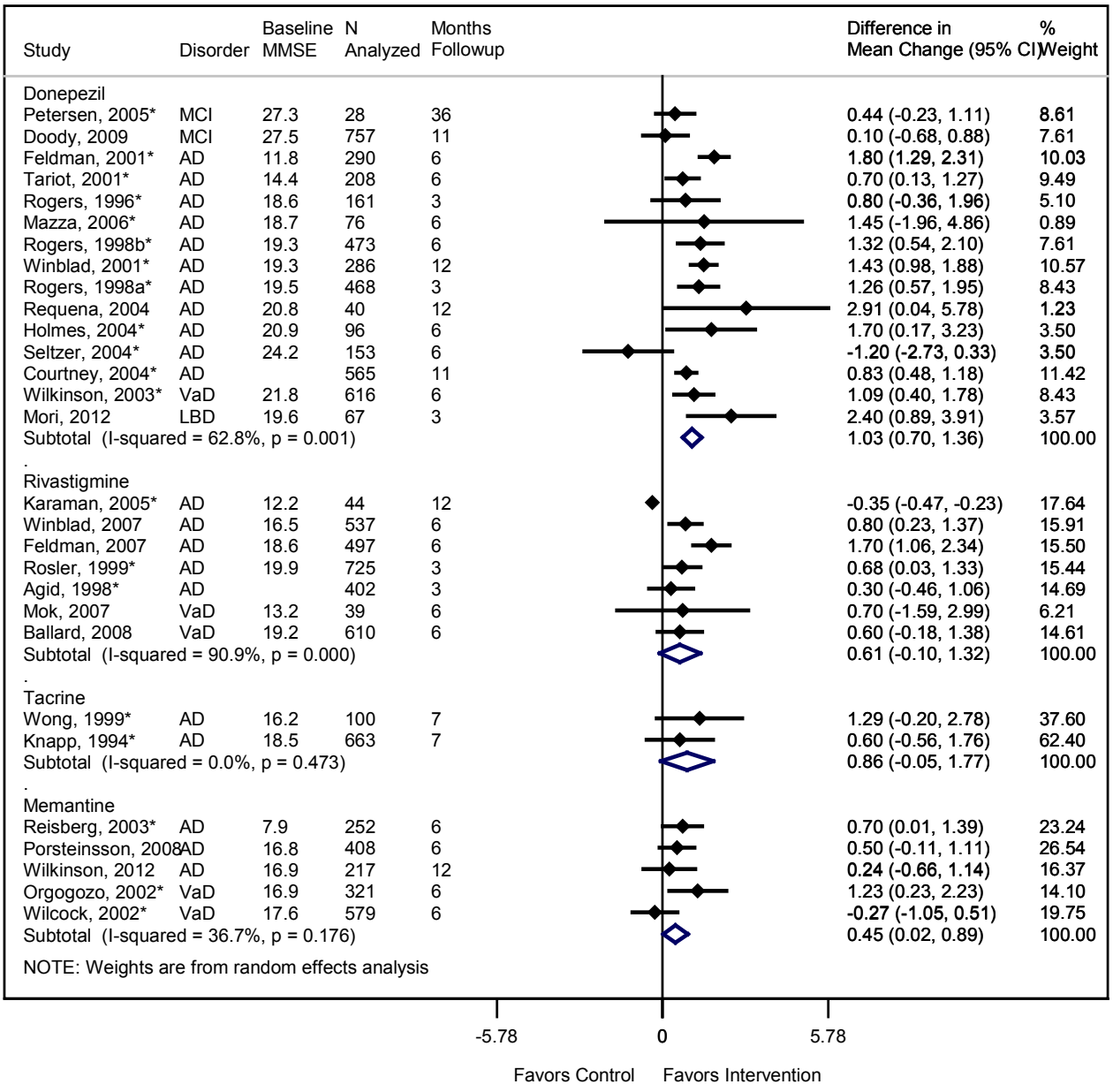
Abbreviations: CI – Confidence interval; F – Full IQCODE; IQCODE – Informant Questionnaire on Cognitive Decline in the Elderly; NR – Not reported; S – Short IQCODE

Figure 8. Meta-Analyses for AChEIs and Memantine on Global Cognitive Function, Measured by the ADAS-Cog (Key Question 4)



*Included in Raina.

Figure 9. Meta-Analyses for AChEIs and Memantine on Global Cognitive Function, Measured by the MMSE (Key Question 4)



*Included in Raina.

Figure 10. Meta-Analyses for AChEIs and Memantine on Withdrawals Due to Adverse Events (Key Question 5)

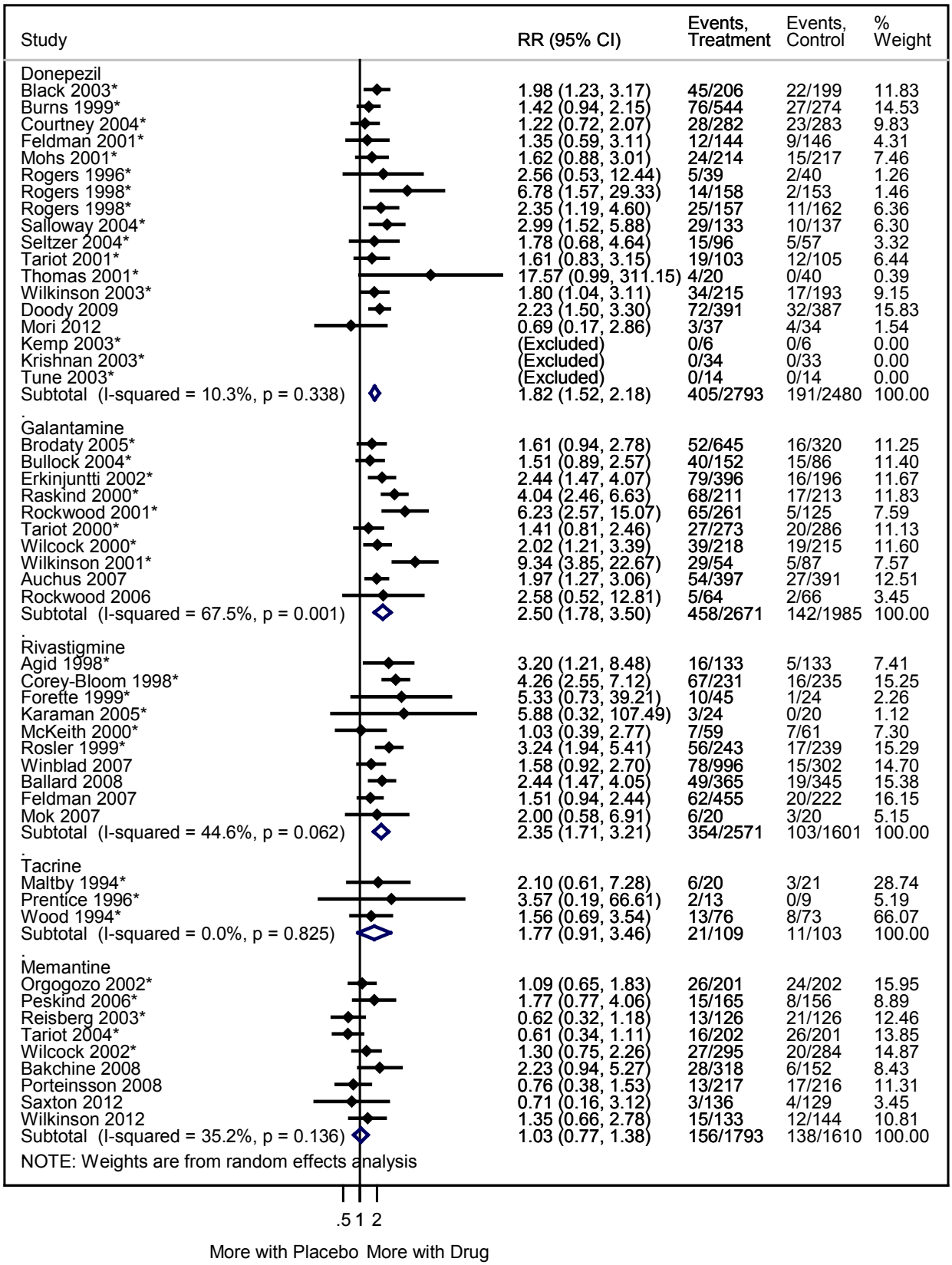
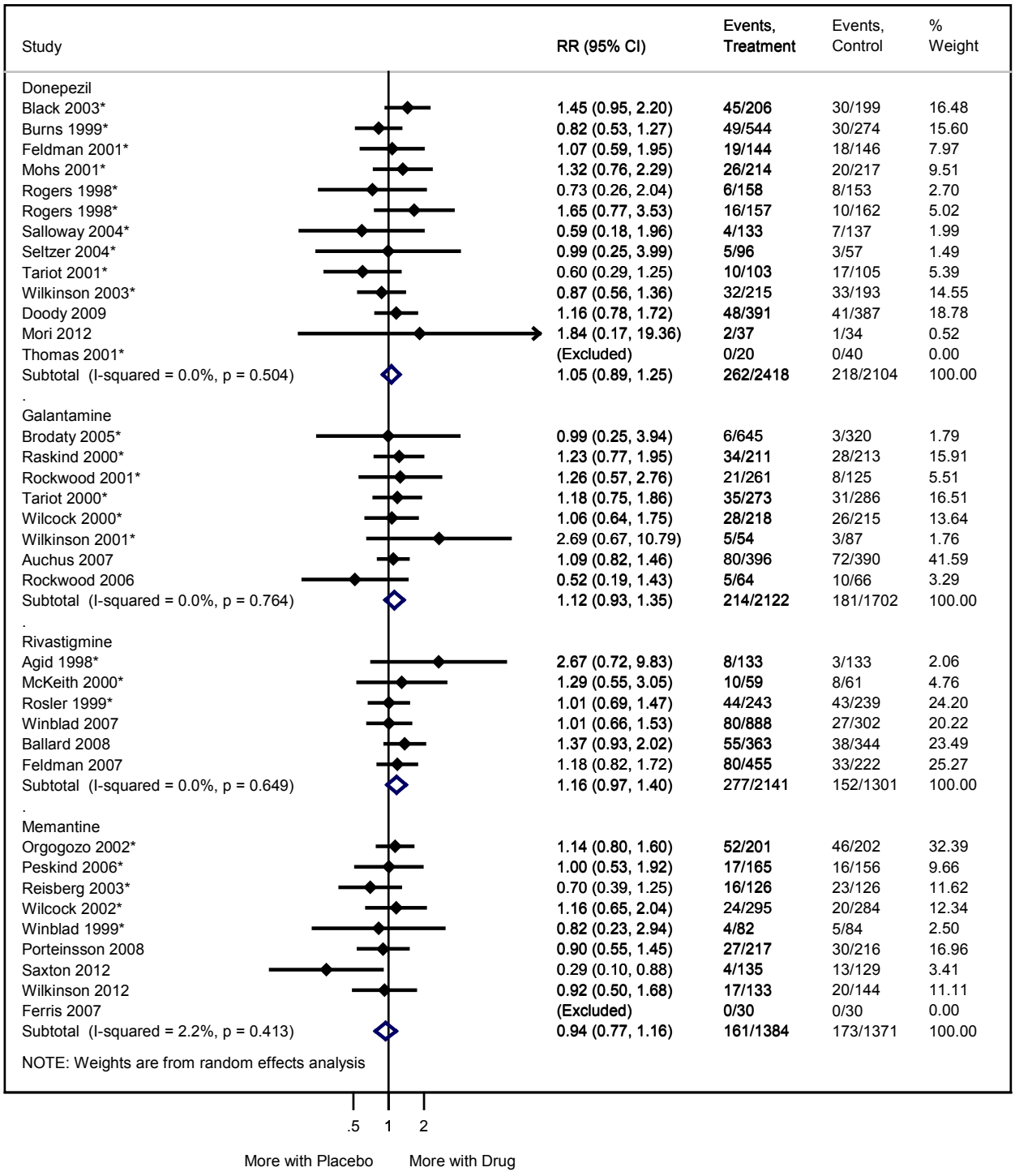
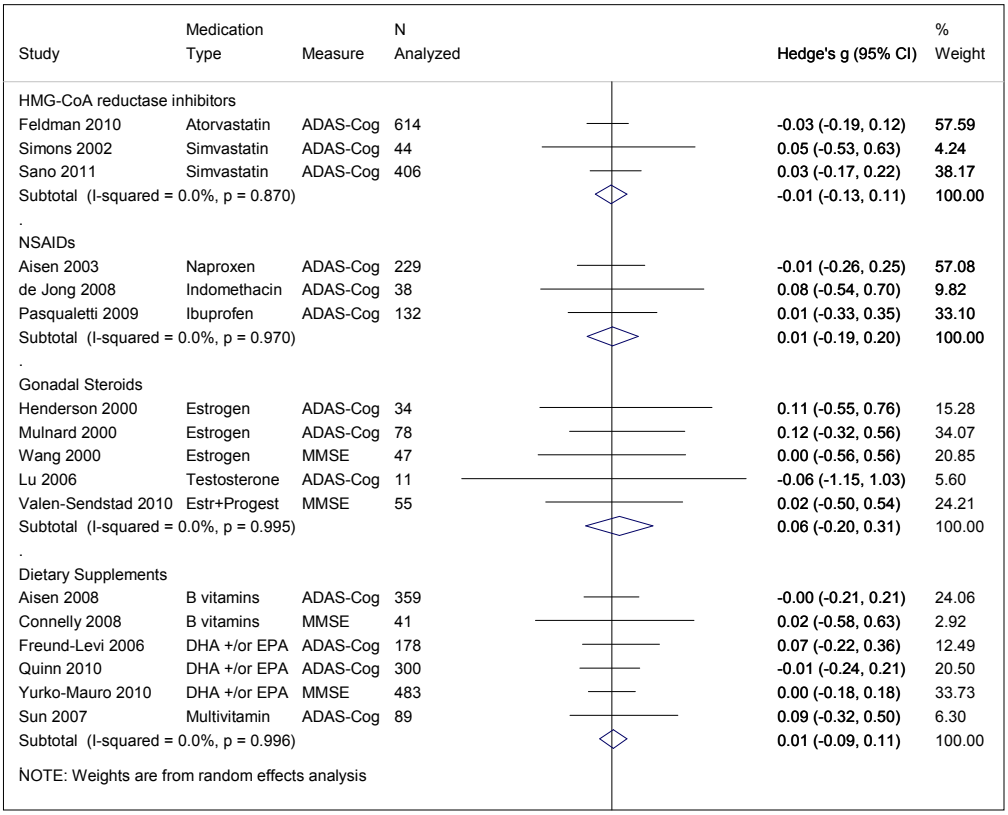


Figure 11. Meta-Analyses for AChEIs and Memantine on Serious Adverse Events (Key Question 5)



*Included in Raina.

Figure 12. Meta-Analyses for Other Medications on Global Cognitive Function, Measured by the ADAS-Cog or MMSE* (Key Question 4)



*MMSE direction has been reversed.

Figure 13. Meta-Analyses for Psychoeducational Caregiver Interventions on Caregiver Burden (Key Question 4)

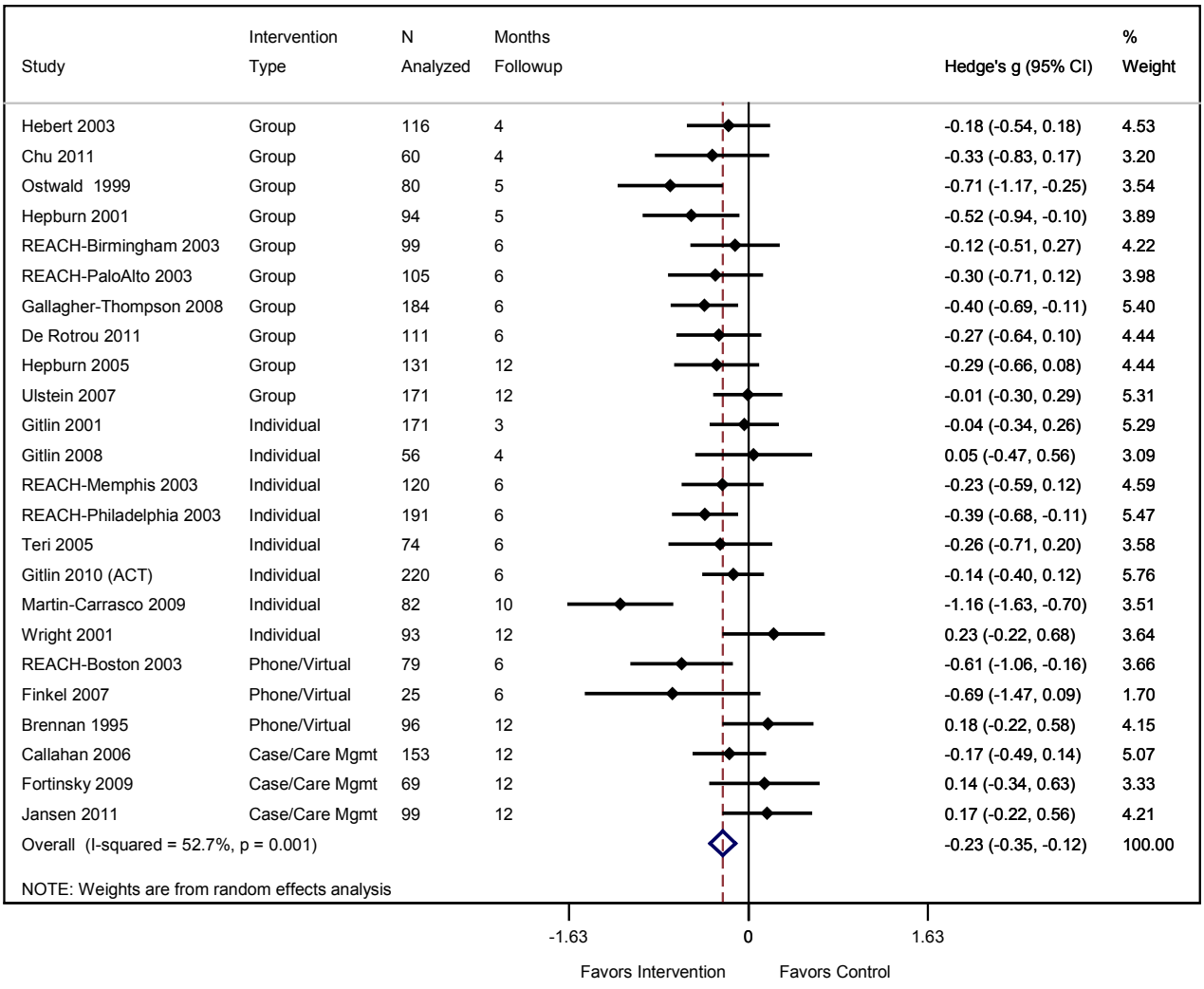


Figure 14. Meta-Analyses for Psychoeducational Caregiver Interventions on Caregiver Depression (Key Question 4)

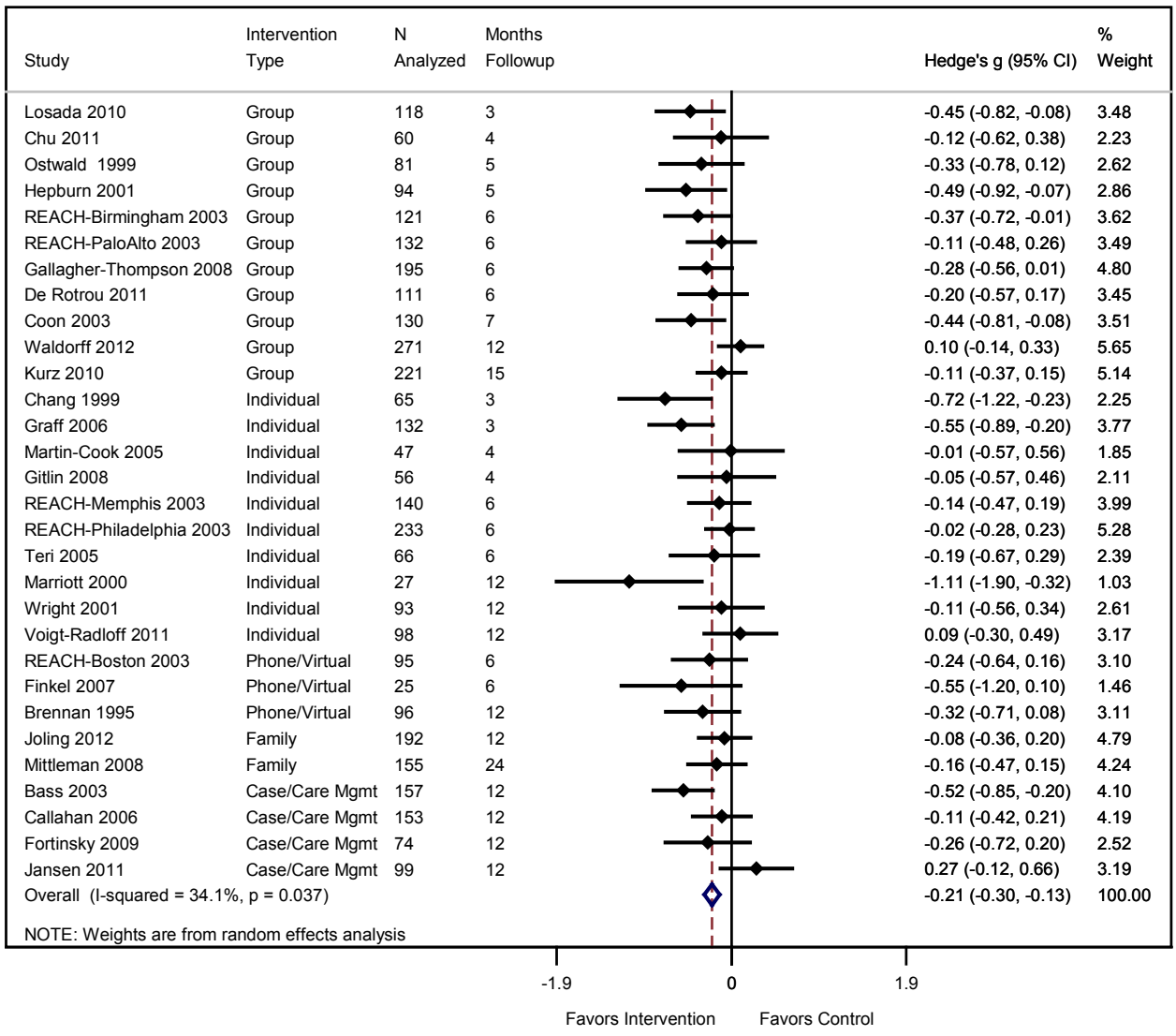
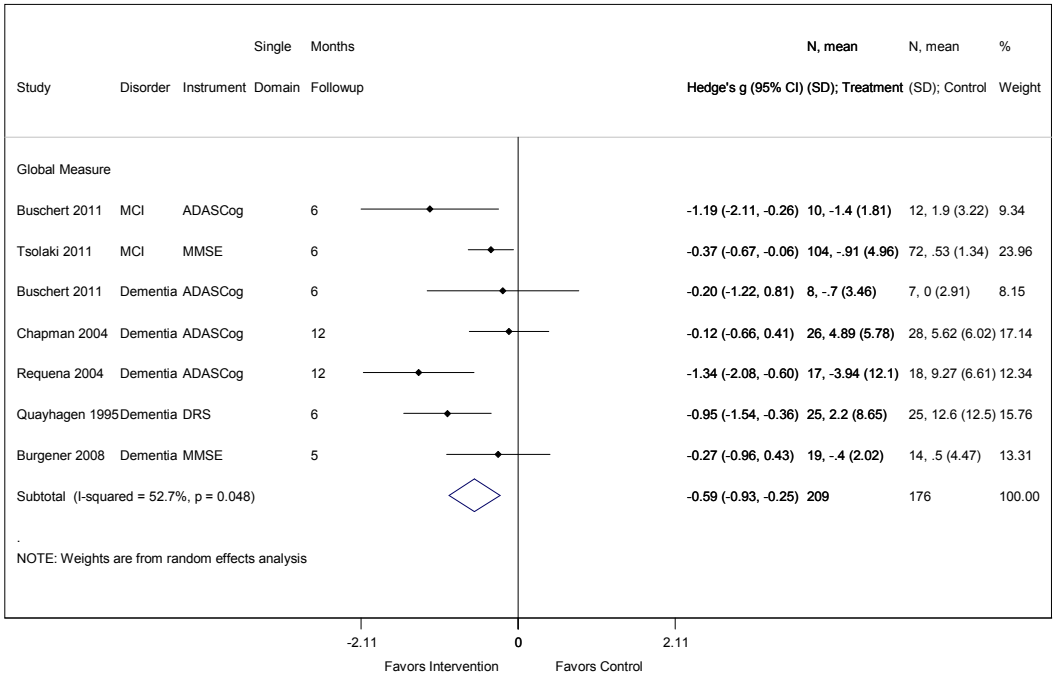


Figure 15. Meta-Analyses for Cognitive Stimulation Interventions on Global Cognitive Function* (Key Question 4)



*All instruments except the ADAS-cog are reversed.

Table 1. Summary of Included Screening Instruments (Alphabetical Order) (Key Question 2)

Instrument	Time to Administer (min)	Informant	Patient	Languages	# of Items	General Description	Memory	Executive Functioning	Aphasia	Apraxia	Agnosia	Total # of Studies	# of Dementia Studies	# of MCI* Studies
3-Word Memory Test	3		x	English	3	3-item recall	x					1	1	0
6-item screener	1-2		x	English	6	3-item recall plus 3 orientation questions	x					1	1	1
7-Minute Screen (7MS)	7		x	English, Spanish	11	Orientation, name objects, recall objects from categories, clock, vegetables	x	x	x	x	x	2	2	0
Abbreviated Mental Test (AMT)	5-7		x	English, Dutch, Bangladeshi, Gujarati, Hindi, Punjabi, Urdu	10	Orientation, memory, name objects, attention tests	x				x	4	4	0
Ascertain Dementia 8 (AD8)	<3	x		English	8	Asks informant about judgment, less interest in hobbies, repeats things, trouble using tools, forgets month or year, finances, trouble remembering appointments or daily things	x	x		x	x	1	0	1
Benton's Orientation Test	<7**		x	Spanish	5	Identify month, date, year, day of the week, and time of day	x					1	1	0
Brief IADL (4IADL)	<5**		x	Chinese or English	4	Independent activities of daily living		x				1	0	1
Clock Drawing Test (CDT)	1-3		x	English, Spanish, German, Korean	1	Clock draw Note: different scoring systems used		x		x		10	7	3
Cognitive Assessment Screening Test (CAST)	15		x	English	28	Memory, orientation, naming, copy a sentence, copy a figure, addition, fill out a check, clock draw, plus multiple questions about memory complaints, changes in behavior	x	x	x	x	x	1	1	0
Computer Assessment of Mild Cognitive Impairment (CAMCI)	NR		x	English	8	Orientation, figure identification, picture recall, word recall, attention, "virtual environment" (follow directions while driving)	x	x		x		1	0	1
Free and Cued Selective Reminding Test (FCSRT)	<7**		x	English, Spanish	16	Controlled learning of a card with 4 pictures; each with a semantic cue; the patient counts backwards by threes for 20 seconds (as interference for working memory) and then has 3 recall trials without then with the semantic cues	x					1	1	0

Table 1. Summary of Included Screening Instruments (Alphabetical Order) (Key Question 2)

Instrument	Time to Administer (min)	Informant	Patient	Languages	# of Items	General Description	Memory	Executive Functioning	Aphasia	Apraxia	Agnosia	Total # of Studies	# of Dementia Studies	# of MCI* Studies
Fuld Object Memory Evaluation, abbreviated	9		x	English, Spanish	10	Participants attempt to identify 10 common items concealed in a bag and are asked to recall the 10 items 3 different times. Each time after identifying the items, participants receive a semantic fluency distractor task for 60, 30, and 30 seconds, respectively	x					1	0	1
Functional Activities Questionnaire (FAQ)	5	x		Spanish	10	Activities and independent activities of daily living, ability to remember appointments, ability to keep track of current events, understanding books	x	x		x		1	1	1
General Practitioner Assessment of Cognition (GPCOG)	4-5	x	x	English	15	Recall, orientation, recent news recall. Patient questionnaire is paired with an informant questionnaire that asks about memory, finances, wordfinding, ADLs	x	x	x			1	1	0
Hopkins Verbal Learning Test (HVLT)	<5**		x	English	12	Immediate recall of objects†	x					2	1	1
Immediate recall	<10**		x	German	10	10 words are given and patient is asked to recall as many as possible; repeated 3 times with the same words but given in different order	x					1	1	0
Immediate Recall (Logical Memory I)	<7**		x	Chinese or English	25	Evaluator reads a story, then asks patient to remember as many things from story as possible	x					1	0	1
Informant Report of Memory Problems (IRMP)	1-2	x		Chinese or English	1	Informant report of memory problems	x					1	0	1
Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Short	NR‡	x		English	16	Same as full IQCODE, except has 16 rather than 26 questions	x	x		x	x	3	2	2

Table 1. Summary of Included Screening Instruments (Alphabetical Order) (Key Question 2)

Instrument	Time to Administer (min)	Informant	Patient	Languages	# of Items	General Description	Memory	Executive Functioning	Aphasia	Apraxia	Agnosia	Total # of Studies	# of Dementia Studies	# of MCI* Studies
IQCODE, Full	NR‡	x		Spanish, English	26	Informant asked to compare patient's current ability with what they remember of patient's ability 10 years ago, such as recognizing faces of family and friends	x	x	x	x	x	4	4	3
Katz ADL	≤5**		x	Finnish	6	Activities of daily living		x		x	x	1	1	0
Kendrick Cognitive tests	<7**		x	English		Recall of outline pictures of common items and speed of copying 10 rows of 10 digits each. Scoring guidelines permit 2 determinations: distinction between dementia and normal and distinction between dementia, depression, and normal	x					1	1	0
Labyrinth Test	<7**		x	German	1	Patient is asked to draw a line that successfully navigates through a maze				x		1	1	0
Lawton IADL	≤5**		x	Finnish	8	Independent activities of daily living		x		x	x	1	1	0
Memory Function 2 (MF-2)	1.5	x	x	English	2	Subjective memory complaints and trouble with executive function Note: This test can be completed by the informant or the patient	x	x				1	1	1
Memory Impairment Screen (MIS)	4		x	English	4	4-item recall, either spontaneous or cued recall	x					4	4	1
Memory Impairment Screen by Telephone (MIS-T)	4		x	English	4	4-item recall, either spontaneous or cued recall	x					1	1	0
Mental Status Questionnaire (MSQ)	4		x	English, Dutch	10	Memory, orientation, naming, attention	x				x	2	2	0
Mini-Cog	3-4		x	English, German	4	3-item recall plus clock draw	x	x		x		4	4	3
Mini-Mental State Examination (MMSE)	7-10		x	English, Spanish, French, Swedish, German, Dutch, Korean, Chinese-Cantonese, Bangladeshi, Gujarati, Hindi, Punjabi, Urdu, Chinese or English, French or English	30	Orientation, recall, naming, draw figure, repetition, attention, reading, writing	x		x	x	x	31	25	14

Table 1. Summary of Included Screening Instruments (Alphabetical Order) (Key Question 2)

Instrument	Time to Administer (min)	Informant	Patient	Languages	# of Items	General Description	Memory	Executive Functioning	Aphasia	Apraxia	Agnosia	Total # of Studies	# of Dementia Studies	# of MCI* Studies
Minimum Data Set Cognition Scale (MDS-Cog)	<10**		x	English	8	Asks about memory awareness of surroundings; decision-making and understanding; and dressing performance in the previous 7 days	x	x			x	1	1	0
MMblind	7-10		x	German	25	Excludes items from MMSE requiring vision: naming, reading, comprehension, copying, writing, and instructions to handle a sheet of paper, resulting in a maximum score of 22	x		x			1	1	0
Montreal Cognitive Assessment (MOCA)	10		x	Korean	30	Trails B, copy figure, clock, naming, verbal fluency, 5-word recall, similarities, orientation, attention	x	x	x	x	x	1	0	1
Oral Trails	4-6**		x	English	2	Asks patient to count out loud from 1 to 25, then alternate between numbers and letters (e.g., 1-A-2-B)		x				1	1	0
Orientation-Memory Concentration (OMC)	5		x	English	6	Memory, orientation, concentration	x					1	1	0
Rey figure copy	<7**		x	English	1	Copy a complex figure first with the drawing then by memory	x	x		x		1	1	0
Self-Administered Gerocognitive Examination (SAGE)	10-15		x	English	14	Memory, orientation, copy figure, change figure, naming, math, similarities, clock draw, animals, trails	x	x	x	x	x	1	1	1
Short Blessed Test (SBT)	2		x	English	6	Memory, orientation, concentration (same as the OMC test)	x					1	1	0
Short Concord Informant Dementia Scale	6-11	x		English	12	Questions for informant about perceived changes in memory and ability to find their way around	x				x	1	1	0
Short Portable Mental Status Questionnaire (SPMSQ)	3-4		x	English, Spanish, Finnish, Dutch	10	Orientation, memory, attention	x					4	4	0
Single-item informant report	1-2	x		English	1	Asks about patient memory	x					1	0	1

Table 1. Summary of Included Screening Instruments (Alphabetical Order) (Key Question 2)

Instrument	Time to Administer (min)	Informant	Patient	Languages	# of Items	General Description	Memory	Executive Functioning	Aphasia	Apraxia	Agnosia	Total # of Studies	# of Dementia Studies	# of MCI* Studies
St. Louis University Mental Status Examination (SLUMS)	7		x	English	30	Orientation, 5-item recall, math, animals, attention, clock, figures, story	x	x	x	x	x	1	0	1
Storandt Battery	10		x	English	2	Word fluency and trailmaking		x	x			1	1	0
Subjective memory impairment	1-2		x	German	1	Yes/No question: Do you feel like your memory is getting worse?	x					1	1	0
Sweet 16	1-3		x	English	16	Orientation (identification of person, place, time, and situation), registration, digit spans (tests of verbal memory), and recall	x					1	1	0
Telephone for Cognitive Status (TICS)	7-9		x	English, Spanish, French	11	Orientation, repetition, naming, and calculations are some of the items covered	x	x				3	2	1
Telephone Iinterview for Cognitive Impairment Modified (TICS-M)	7-9		x	English, French, English or Spanish	13	Similar to TICS	x	x				3	0	3
Trailmaking A and B	1-2 (A), 2-4 (B)		x	German		Different versions have patients go to different numbers/letters		x				3	2	1
Verbal fluency	1-3		x	English, Spanish, German	1	Name as many animals, first names, or similar objects as possible in 1 minute			x			6	6	0
Visual Association (VAT)	4-6		x	German	12	Visual association and recall	x			x		1	1	0
Word List Learning	<7**		x	German	8	Immediate and delayed recall and recognition tasks (delay 20 min). Recognition task is composed of 8 targets and 8 distractors	x					1	1	0

* Includes studies that screened for MCI only as well as studies that screened for MCI or dementia (MCI and dementia results not separated).
** Assumed.
† This test typically includes a delayed recall component as well as an immediate recall. Only the immediate recall was included due to time.
‡ Reported administration times varied, but the IQCODE can be self-administered in less than 20 minutes, so was included.

Abbreviations: ADL = activities of daily living; IADL = instrumental activities of daily living; MCI = mild cognitive impairment; NR = not reported.

Table 2. Summary Table: Screening for Dementia (Dementia vs. MCI/Normal), Very Brief Instruments (Key Question 2)

Instrument	Study	Quality	Country	N Screened, N Analyzed	Selection Criteria	Age (y)	% Female	Education (y)	% Dementia	Cut-point	Outcomes
CDT	Fuchs, 2011[161]	Fair	DE	423 423	75-89 y PC	82.4	68.4	62.2% "low" level	5.0	NR	Se, Sp, PPV, NPV, AUC
CDT	Kirby, 2001[169]	Fair	IE	648 648	≥65 y PC	75.0	NR	10.8	6.3	<6	Se, Sp, PPV, NPV
CDT*	Ball, 2001[167]	Fair	US	170 53	≥65 y Female Community	76.3	100	13.6	9	NR	Se, Sp
CDT	Del Ser, 2006[162]	Fair	ES	527 416	≥65 y Community	79	51.7	63% <primary school	11.5	NR	Se, Sp, PPV, NPV, AUC
CDT	Grober, 2008[168]	Good	US	318 318	≥65 y NonHispanic white or black PC	78.7	83	12.6	17.6	13	Se, Sp, PPV, NPV
CDT	Wolf-Klein, 1989[171]	Good	US	325 312	Geriatric health center	76.8	70.5	NR	47.1	NR	Se, Sp, PPV, NPV
Mini-Cog	Holsinger, 2012[173]	Good	US	639 630	≥65 y PC	74.8	7.1	13.0	3.3	2/3	Se, Sp, PPV, NPV
Mini-Cog	Fuchs, 2011[161]	Fair	DE	423 423	75-89 y PC	82.4	68.4	62.2% "low" level	5.0	NR	Se, Sp, PPV, NPV, AUC
Mini-Cog	Kaufer, 2008[152]	Fair	US	146 146	≥65 y Residential care/assisted living	83.4	79	Majority ≥high school	38	0	Se, Sp, PPV, NPV
Mini-Cog	Borson, 2006[172]	Fair	US**	371 371	Community	NR	NR	NR	40.2	2/3	Se, Sp, PPV, NPV
MIS	Holsinger, 2012[173]	Good	US	639 630	≥65 y PC	74.8	7.1	13.0	3.3	4/5	Se, Sp, PPV, NPV
MIS-T	Lipton, 2003[176]	Fair	US	300 300	≥65 y PC	79.3	66.0	12.8	9	4	Se, Sp, PPV, NPV, AUC
MIS	Buschke, 1999[174]	Fair	US	483 483	≥65 y Senior centers; PC	79.5	64	12.1	10.4	4	Se, Sp, PPV, NPV, AUC
MIS	Kuslansky, 2002[175]	Fair	US	240 240	≥70 y PC	78.7	64.1	12.5	11.7	4	Se, Sp, PPV, NPV, AUC
MIS	Grober, 2008[168]	Good	US	318 318	≥65 y NonHispanic white or black PC	78.7	83	12.6	17.6	4	Se, Sp, PPV, NPV

Table 2. Summary Table: Screening for Dementia (Dementia vs. MCI/Normal), Very Brief Instruments (Key Question 2)

Instrument	Study	Quality	Country	N Screened, N Analyzed	Selection Criteria	Age (y)	% Female	Education (y)	% Dementia	Cut-point	Outcomes
SPMSQ	Erkinjuntti, 1987[155]	Fair	FI	119 119	≥65 y Community	73	65	85% ≤grade school	2.5	7/8	Se, Sp, PPV, NPV
SPMSQ	Hooijer, 1992[178]	Fair	NL	358 358	Older adults PC	NR	NR	NR	3.6	7/8	Se, Sp, PPV, NPV
MSQ	Hooijer, 1992[178]	Fair	NL	358 358	Older adults PC	NR	NR	NR	3.6	7/8	Se, Sp, PPV, NPV
SPMSQ	Del Ser, 2006[162]	Fair	ES	527 416	≥65 y Community	79	51.7	63% <primary school	11.5	NR	Se, Sp, PPV, NPV, AUC
SPMSQ	Fillenbaum, 1990[177]	Fair	US	164 164	≥65 y Community	NR	57.9	NR	16.4	NR	Se, Sp, PPV, NPV
MSQ	Fillenbaum, 1990[177]	Fair	US	164 164	≥65 y Community	NR	57.9	NR	16.4	7/8	Se, Sp, PPV, NPV
Verbal fluency–animals	Fuchs, 2011[161]	Fair	DE	423 423	75-89 y PC	82.4	68.4	62.2% “low” level	5.0	≤12	Se, Sp, PPV, NPV, AUC
Category Fluency Telephone–animals and fruits	Lipton, 2003[176]	Fair	US	300 300	≥65 y PC	79.3	66.0	12.8	9	13, 15, 19	Se, Sp, PPV, NPV, AUC
Verbal fluency–category	Del Ser, 2006[162]	Fair	ES	527 416	≥65 y Community	79	51.7	63% <primary school	11.5	NR	Se, Sp, PPV, NPV, AUC
Verbal fluency–animals	Heun, 1998[179]	Fair	DE	291 287	60-100 y Community	76.6	59.9	9.5	12.9	≤14	Se, Sp, PPV, NPV, AUC
Verbal fluency–first names	Heun, 1998[179]	Fair	DE	291 287	60-100 y Community	76.6	59.9	9.5	12.9	≤14	Se, Sp, PPV, NPV, AUC
Verbal fluency–animals	Grober, 2008[168]	Good	US	318 318	≥65 y NonHispanic white or black PC	78.7	83	12.6	17.6	12 14	Se, Sp, PPV, NPV

* Authors called their test the Clock Completion Test.
** Administered in the primary language of the participant.

Abbreviations: AUC = area under the curve; CDT = Clock Drawing Test; DE = Germany; ES = Spain; FI = Finland; IE = Ireland; MCI = mild cognitive impairment; MIS = Memory Impairment Screen; MIS-T = Memory Impairment Screen by Telephone; MSQ = Mental Status Questionnaire; NL = Netherlands; NPV = negative predictive value; NR = not reported; PC = primary care; PPV = positive predictive value; Se = standard error; Sp = specificity; SPMSQ = Short Portable Mental Status Questionnaire.

Table 3. Summary Table: Screening for Dementia (Dementia vs. MCI/Normal), Brief Instruments (Key Question 2)

Instrument	Study	Quality	Country	N Screened, N Analyzed	Selection Criteria	Age (y)	% Female	Education (y)	% Dementia	Cut-point	Outcomes
AMT	Brodaty, 2002[154]	Fair	AU	283 269	50-74 y (w/memory problem) or ≥75 y PC	79.6	59.4	55.8% >8 y	29	7/8	Se, Sp, PPV, NPV, AUC
AMT	Hooijer, 1992[178]	Fair	NL	358 358	Older adults PC	NR	NR	NR	3.6	7/8	Se, Sp, PPV, NPV
AMT	Rait, 2000[181]	Fair	UK	130 96	≥60 y Jamaican PC	69	50	9	6	≥8	Se, Sp, PPV, NPV
AMT	Rait, 2000[182]	Fair	UK (Bangladeshi, Gujarati, Hindi Punjabi, Urdu)	120 101	≥60 y Gujarati or Pakistani PC	69.2	52.5	NR	11	6 Gujarati 7 Pakistani	Se, Sp
FCSRT	Grober, 2008[168]	Good	US	318 318	≥65 y NonHispanic white or black PC	78.7	83	12.6	17.6	25	Se, Sp, PPV, NPV
FCR	Del Ser, 2006[162]	Fair	ES	527 416	≥65 y Community	79	51.7	63% <primary school	11.5	NR	Se, Sp, PPV, NPV, AUC
7MS	Del Ser, 2006[162]	Fair	ES	527 416	≥65 y Community	79	51.7	63% <primary school	11.5	NR	Se, Sp, PPV, NPV, AUC
7MS	Solomon, 2000[183]	Fair−	US	137 137	≥60 y PC	77.0	67.2	11.8	8.0	0.3/0.7 (no patients scored between 0.3 & 0.7)	Se, Sp, PPV, NPV
TICS	Manly, 2011[184]	Fair	US (English or Spanish)	377 377	≥65 y PC	81.4	68.2	10.4	14.1	≤22	Se, Sp, PPV, NPV, AUC
TICS	Lipton, 2003[176]	Fair+	US	300 300	≥65 y PC	79.3	66.0	12.8	9	28	Se, Sp, PPV, NPV, AUC
MMSE	Brodaty, 2002[154]	Fair	AU	283 283	50-74 y (w/memory problem) or ≥75 y PC	79.6	59.4	55.8% >8 y	29	24/25 (23/24 reported in text)	Se, Sp, PPV, NPV, AUC
MMSE	Callahan, 2002[185]	Fair−	US	2212 269	≥65 y Black Community	74.4	59.4	10.4	4.3	≤24	Se, Sp, PPV, NPV, AUC
MMSE	Cruz-Orduna, 2011[160]	Fair	ES	160 160	Cognition-related complaint PC	72.4	70	88.8% ≤primary school	9.4	18/19	Se, Sp, PPV, NPV, AUC

Table 3. Summary Table: Screening for Dementia (Dementia vs. MCI/Normal), Brief Instruments (Key Question 2)

Instrument	Study	Quality	Country	N Screened, N Analyzed	Selection Criteria	Age (y)	% Female	Education (y)	% Dementia	Cut-point	Outcomes
MMSE	Cullen, 2005[186]	Fair−	IE	1142 1115	≥65 y PC	74.8	68	9.9	3.9	<24	Se, Sp, PPV, NPV
MMSE	Fillenbaum, 1990[177]	Fair−	US	164 164	≥65 y Community	NR	57.9	NR	16.4	NR	Se, Sp, PPV, NPV
MMSE	Fong, 2011[187]	Fair	US	709 709	≥70 y Community	78.8	60	NR	1.2	<24	Se, Sp, PPV, NPV, AUC
MMSE	Gagnon, 1990[157]	Fair−	FR	2730 2730	≥65 y Community	74.6	59.4	66% ≤primary school	3.7	24	Se, Sp, PPV, NPV
MMSE	Grut, 1993[158]	Fair−	SE	1810 668	>74 y Community	NR	76.1	46.1% ≥high school	14.1	24/25	Se, Sp, PPV
MMSE	Heun, 1998[179]	Fair+	DE	291 287	60-100 y Community	76.6	59.9	9.5	12.9	≤24	Se, Sp, PPV, NPV, AUC
MMSE	Hooijer, 1992[178]	Fair	NL	358 358	Older adults PC	NR	NR	NR	3.6	23/24	Se, Sp, PPV, NPV
MMSE	Jeong, 2004[163]	Good	KR	235 235	≥65 y Community	73.5	66.4	1 (median)	19.6	18/19	Se, Sp, PPV, NPV, AUC
MMSE	Jorm, 1996[188]	Fair	AU	144 143	POW/veteran	72.9	0	NR	NR	26/27	Se, Sp, AUC
MMSE	Kahle-Wrobleski, 2007[189]	Fair−	US	435 435	≥90 y Retirement community	95	74	73% >12 y	36	24	Se, Sp, PPV, NPV, AUC
MMSE	Kaufer, 2008[152]	Fair	US	146 146	≥65 y Residential care/assisted living	83.4	79	majority with ≥high school	38	<27	Se, Sp, PPV, NPV, AUC
MMSE	Kay, 1985[190]	Fair	AU	274 274	≥70 y Community	NR (158 were 70-79, 116 were 80+)	63.5		14.2	24/25	Se, Sp, PPV, NPV
MMSE	Kirby, 2001[169]	Fair	IE	648 648	≥65 y PC	75.0	NR	10.8	6.3	<24	Se, Sp, PPV, NPV
MMSE	Lavery, 2007[170]	Fair	US	1107 339	≥65 y PC	77.5	68.7	66.8% ≥12 y	9.7	≥22	Se, Sp, PPV, NPV, AUC
MMSE	McDowell, 1997[159]	Fair	CA (English or French)	1600 1600	≥65 y	80.0	59	8.6	23	24	Se, Sp, PPV, NPV, AUC

Table 3. Summary Table: Screening for Dementia (Dementia vs. MCI/Normal), Brief Instruments (Key Question 2)

Instrument	Study	Quality	Country	N Screened, N Analyzed	Selection Criteria	Age (y)	% Female	Education (y)	% Dementia	Cut-point	Outcomes
MMSE	Morales, 1997[165]	Fair	ES	257 (97 urban, 160 rural) 257	≥65 y (urban); ≥60 y (rural) Community	74.1	61.9	4.9	13.2	21 (urban) 20 (rural)	Se, Sp, PPV, NPV
MMSE	Rait, 2000[181]	Fair	UK	130 96	≥60 y Jamaican PC	69	50	9	6	≥27	Se, Sp, PPV, NPV
MMSE	Rait, 2000[182]	Fair	UK (Bangladeshi, Gujarati, Hindi Punjabi, Urdu)	120 101	≥60 y Gujarati or Pakistani PC	69.2	52.5	NR	11	24 Gujarati 27 Pakistani	Se, Sp
MMSE	Reischies, 1997[191]	Fair−	DE	516 449	≥70 y Community	NR	NR	NR	19.4	24/25	Se, Sp, PPV, NPV
MMSE	Scharre, 2010[153]	Fair−	US	254 63	>59 y Geriatric outpatient; community; independent and assisted living facilities; senior centers; memory clinic	78	66.7	93.7% ≥high school	33	≤26	Se, Sp, PPV, NPV, AUC
MMSE	Waite, 1998[192]	Fair	AU	630 360	≥75 y Community; veterans	83.9	54.8	10	27.5	23/24	Se, Sp, PPV, NPV, AUC

Abbreviations: AMT = Abbreviated Mental Test; AU = Australia; AUC = area under the curve; CA = Canada; DE = Germany; ES = Spain; FCR = Free and Cued Recall; FCSRT = Free and Cued Selective Reminding Test; FR = France; IE = Ireland; KR = South Korea; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NL = Netherlands; NPV = negative predictive value; NR = not reported; PC = primary care; POW = prisoner of war; PPV = positive predictive value; SE = Sweden; Se = standard error; Sp = specificity; TICS = Telephone Interview for Cognitive Status; UK = United Kingdom; 7MS = 7-Minute Screen.

Table 4. Summary Table: Screening for Dementia (Dementia vs. MCI/Normal), Self-Administered Instruments (Key Question 2)

Instrument	Study	Quality	Country	N Screened, N Analyzed	Selection Criteria	Age (y)	% Female	Education (y)	% Dementia	Cut-point	Outcomes
Short IQCODE	Grober, 2008[168]	Good	US	318 318	≥65 y NonHispanic white or Black PC	78.7	83	12.6	17.6	3.3	Se, Sp, PPV, NPV
Short IQCODE	Jorm, 1996[188]	Fair	AU	144 143	POW/veterans	72.9	0	NR	NR	3.31/ 3.38	Se, Sp, AUC
Full IQCODE	Cruz-Orduna, 2011[160]	Fair	ES	160 160	Cognition-related complaint PC	72.4	70	88.8% ≤primary school	9.4	3.65/ 3.69	Se, Sp, PPV, NPV, AUC
Full IQCODE	Morales, 1997[165]	Fair	ES	257 (97 urban, 160 rural) 257	≥65 y (urban); ≥60 y (rural) Community	74.1	61.9	4.9	13.2	3.27 (urban) 3.31 (rural)	Se, Sp, PPV, NPV
Full IQCODE	Jorm, 1996[188]	Fair	AU	144 143	POW/veterans	72.9	0	NR	NR	3.27/ 3.30	Se, Sp, AUC
Full IQCODE	Tokuhara, 2006[195]	Fair+	US	299 230 (N analyzed unclear)	≥65 y Japanese/Okinawan PC	74.2	66	12.2	7	3.5	Se, Sp, PPV, NPV
SAGE	Scharre, 2010[153]	Fair−	US	254 63	>59 y Geriatric outpatient; community; independent and assisted living facilities; senior centers; memory clinic	78	66.7	93.7% ≥high school	33	≤14	Se, Sp, PPV, NPV, AUC

Abbreviations: AU = Australia; AUC = area under the curve; ES = Spain; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; MCI = mild cognitive impairment; NPV = negative predictive value; PC = primary care; PPV = positive predictive value; SAGE = Self-Administered Gerocognitive Examination; Se = standard error; Sp = specificity.

Table 5. Summary Table: Screening for Mild Cognitive Impairment (MCI vs. Normal, Dementia Not Included), Very Brief Instruments (Key Question 2)

Instrument	Study	Quality	Country	N Screened, N Analyzed	Selection Criteria	Age (y)	% Female	Education (y)	% Dementia, % MCI	Cut-point	Outcomes
CDT	Donnelly, 2008[202]	Fair	US	100 100	≥65 y PC	77.9	1	12.9	NA 20	1 SD	Se, Sp, PPV, NPV, AUC
CDT	Ehreke, 2009[198]	Fair	DE	3198 3198	≥75 y PC	80.1	65.4	61.8% "low" level	NA 15.0 (original) 24.6 (modified)	9	Se, Sp, PPV, NPV, AUC
CDT	Ehreke, 2011[196]	Fair	DE	428 428	≥75 y Community and institutions	83	73	63.5% "low" education	NA 13.6	≥2 (Shulman) ≤9 (Ihl and Sunderland) ≤7 (Rouleau) ≤15 (Babins) ≤18 (Mendez) ≤2 (Lin)	Se, Sp, PPV, NPV
CDT	Lee, 2008[199]	Fair	KP	465 465	≥60 y Hospital outpatients; community	71.0	63.4	53.1% <primary school	NA 48.2	9/10 (Freedman) 6/6.5 (Todd) 7/8 (Rouleau) 1/2 (CERAD}	Se, Sp, PPV, NPV, AUC
Mini-Cog	Kaufer, 2008[152]	Fair	US	146 91	≥65 y Residential care/assisted living facilities	83.4	79	Majority >high school	NA 83.5	0	Se, Sp, PPV, NPV, AUC
Mini-Cog	Borson, 2006[172]	Fair	US (primary language spoken)	371 371	Community	NR	NR	NR	40.2 12.1	2/3	Se, Sp, PPV, NPV
Mini-Cog	Holsinger, 2012[173]	Good	US	639 630	≥65 y PC	74.8	7.1	NR	3.3 39.2	2/3	Se, Sp, PPV, NPV

Abbreviations: AUC = area under the curve; CDT = Clock Drawing Test; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; DE = Germany; MCI = mild cognitive impairment; KP = South Korea; NA = not applicable; NPV = negative predictive value; NR = not reported; PC = primary care; PPV = positive predictive value; SD = standard deviation; Se = standard error; Sp = specificity.

Table 6. Summary Table: Screening for Mild Cognitive Impairment (MCI vs. Normal, Dementia Not Included), Brief Instruments (Key Question 2)

Instrument	Study	Quality	Country	N Screened, N Analyzed	Selection Criteria	Age (y)	% Female	Education (y)	% Dementia, % MCI	Cut-point	Outcomes
TICS-M	Cook, 2009[204]	Fair	US	71 71	≥65 y Community	74.9	56.3	16.1	NA 23.9	26 31 34	Se, Sp, PPV, NPV, AUC
TICS-M	Manly, 2011[184]	Fair	US (English or Spanish)	377 377	≥65 y PC	81.4	68.2	10.4	14.1 18.0	≤26	Se, Sp, PPV, NPV, AUC
TICS-M	Vercambre, 2010[203]	Fair	FR	120 120	Born between 1925 and 1930 Women National Education System	78.8	100	NR	8.3 (probable and possible) 15	27 31 34	Se, Sp, PPV, NPV, AUC
MMSE	Donnelly, 2008[202]	Fair	US	100 100	≥65 y PC	77.9	1	12.9	NA 20	1 SD	Se, Sp, PPV, NPV, AUC
MMSE	Kaufer, 2008[152]	Fair	US	146 91	≥65 y Residential care/assisted living facilities	83.4	79	Majority >high school	NA 83.5	<28	Se, Sp, PPV, NPV, AUC
MMSE	Rideaux, 2012[205]	Fair	US	701 522	≥70 y Community	81	55	10.3	25.5 31.7	<26 (white) <23 (black) <25 (Latino)	Se, Sp, PPV, NPV
MMSE	Saxton, 2009[200]	Good	US	524 524	≥60 y PC; Senior community centers	73.3	65.1	13.46	NA 43.5	28	Se, Sp, PPV, NPV
MMSE	Scharre, 2010[153]	Fair	US	254 42	>59 y Geriatric outpatient; community; independent & assisted living facilities; senior centers; memory clinic	78	66.7	93.7% ≥high school	NA 50	NR	Se, Sp, PPV, NPV, AUC
MMSE	Tariq, 2006[134]	Fair	US	702 620	≥60 y VA	75.3	NR	69.4% ≥high school	NA 29.0	28.5 (<high school education) 29.5 (≥high school education)	Se, Sp, PPV, NPV, AUC
MoCA	Lee, 2008[133]	Fair	KP	196 152	≥65 y Community and hospital outpatients	70	65	9.7% >12 yy	22.4 18.9	25/26	Se, Sp, PPV, NPV, AUC
MoCA	Markwick, 2012[201]	Good	UK	107 99	NR	76	54	76.6% >12 y	7.5 18.7	<26	Se, Sp, PPV, NPV

Abbreviations: AUC = area under the curve; FR = France; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NA = not applicable; NPV = negative predictive value; NR = not reported; PC = primary care; PPV = positive predictive value; SD = standard deviation; Se = standard error; Sp = specificity; TICS-M = Telephone Interview for Cognitive Impairment, Modified; VA = Veterans Affairs.

Table 7. Summary Table: Screening for Mild Cognitive Impairment (MCI vs. Normal, Dementia Not Included), Self-Administered Instruments (Key Question 2)

Instrument	Study	Quality	Country	N Screened, N Analyzed	Selection Criteria	Age (y)	% Female	Education (y)	% Dementia, % MCI	Cut-point	Outcomes
Short IQCODE	Ayalon, 2011[135]	Fair−	US	856 441	≥70 y PC	80.3	55.6	11.2	NA 42.0	>3	Se, Sp, PPV, NPV, AUC
Full IQCODE	Cruz-Orduna, 2011[160]	Fair	ES	160 160	Cognition-related complaint PC	72.4	70	88.8% <primary school	9.4 46.9	3.31/3.35	Se, Sp, PPV, NPV, AUC
Full IQCODE	Tokuhara, 2006[195]	Fair	US	299 230	≥65 y Japanese/Okinawan PC	74.2	66	12.2	7 10	3.3	Se, Sp, AUC

Abbreviations: AUC = area under the curve; ES = Spain; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; MCI = mild cognitive impairment; NA = not applicable; NPV = negative predictive value; PC = primary care; PPV = positive predictive value; Se = standard error; Sp = specificity.

Table 8. Summary Table: Screening for Cognitive Impairment (MCI/Dementia vs. Normal), Very Brief Instruments (Key Question 2)

Instrument	Study	Quality	Country	N Screened, N Analyzed	Selection Criteria	Age (y)	% Female	Education (y)	% Dementia, % MCI	Cut-point	Outcomes
Mini-Cog (primary language spoken)	Borson, 2006[172]	Fair	US	371 371	Community	NR	NR	NR	40.2 12.1	2/3	Se, Sp, PPV, NPV
Mini-cog	Holsinger, 2012[173]	Good	US	639 630	≥65 y PC	74.8	7.1	NR	3.3 39.2	2/3	Se, Sp, PPV, NPV
MIS	Holsinger, 2012[173]	Good	US	639 630	≥65 y PC	74.8	7.1	NR	3.3 39.2	2/3	Se, Sp, PPV, NPV

Abbreviations: MIS = Memory Impairment Screen; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; PC = primary care; Se = sensitivity; Sp = specificity.

Table 9. Summary Table: Screening for Cognitive Impairment (MCI/Dementia vs. Normal), Brief Instruments (Key Question 2)

Instrument	Study	Quality	Country	N Screened, N Analyzed	Selection Criteria	Age (y)	% Female	Education (y)	% Dementia, % MCI	Cut-point	Outcomes
TICS (French)	Vercambre, 2010[203]	Fair	FR	120 120	Born between 1925 and 1930 Women National Education System	78.8	100	NR	8.3 (probable and possible) 15	NR	AUC
TICS-M (English or Spanish)	Manly, 2011[184]	Fair	US	377 377	≥65 y PC	81.4	68.2	10.4	14.1 18.0	≤26	Se, Sp, PPV, NPV, AUC
TICS-M (French)	Vercambre, 2010[203]	Fair	FR	120 120	Born between 1925 and 1930 Women National Education System	78.8	100	NR	8.3 (probable and possible) 15	27 31 34	Se, Sp, PPV, NPV, AUC
MMSE	Callahan, 2002[185]	Fair	US	2212 269	≥65 y Black Community	74.4	59.4	12.1	4.3 26.4	23/24 24/25	Se, Sp, PPV, NPV, AUC
MMSE (Spanish)	Cruz-Orduna, 2011[160]	Fair	ES	160 160	Cognition-related complaint PC	72.4	70	% None/Incomplete: 44.4 % Primary: 44.4 % Superior: 5.6	9.4 46.9	23/24	Se, Sp, PPV, NPV, AUC
MMSE	Cullen, 2005[186]	Fair	IE	1142 1115	≥65 y PC	74.8	68	9.9	3.9 4.8	23/24	Se, Sp, PPV, NPV
MMSE (Korean)	Jeong, 2004[163]	Good	KP	235 235	≥65 y Community	73.5	66.4	1 (median)	19.6 23.0	20/21	Se, Sp, PPV, NPV, AUC
MMSE	Jorm, 1996[188]	Fair	AU	144 NR	POW/veteran	72.9	0	NR	NR NR	NR	AUC
MMSE (Chinese)	Lam, 2008[164]	Fair	HK	459 459	Community	71.2	54.5	4.8	9.6 35.3	NR	AUC
MMSE (Chinese or English)	Li, 2006[197]	Fair	SI	144 NR	65-90 y Community; neuroscience clinic	72.7	50.7	4.7	13.2 25.7	NR	AUC
MMSE (English or French)	McDowell, 1997[159]	Fair	CA	1600 1600	≥65 y Community	80.0	59	8.6	23 30	NR	AUC
MMSE	Scharre, 2010[153]	Fair	US	254 63	>59 y Geriatric outpatient; community; independent and assisted living facilities; senior centers; memory clinic	78	66.7	93.7% ≥high school	33 33	≤27	Se, Sp, PPV, NPV, AUC

Table 9. Summary Table: Screening for Cognitive Impairment (MCI/Dementia vs. Normal), Brief Instruments (Key Question 2)

Instrument	Study	Quality	Country	N Screened, N Analyzed	Selection Criteria	Age (y)	% Female	Education (y)	% Dementia, % MCI	Cut-point	Outcomes
MMSE (French)	Vercambre, 2010[203]	Fair	FR	120 120	Born between 1925 and 1930 Women National Education System	78.8	100	NR	8.3 15	NR	AUC

Abbreviations: AU = Australia; AUC = area under the curve; CA = Canada; ES = Spain; FR = France; HK = Hong Kong; IE = Ireland; KP = South Korea; MMSE = Mini-Mental State Examination; NPV = negative predictive value; NR = not reported; POW = prisoner of war; PPV = positive predictive value; Se = sensitivity; SI = Singapore; Sp = specificity; TICS = Telephone Interview for Cognitive Impairment; TICS-M = Telephone Interview for Cognitive Impairment, Modified.

Table 10. Summary Table: Screening for Cognitive Impairment (MCI/Dementia vs. Normal), Self-Administered Instruments (Key Question 2)

Instrument	Study	Quality	Country	N Screened, N Analyzed	Selection criteria	Age (y)	% Female	Education (y)	% Dementia, % MCI	Cut-point	Outcomes
Short IQCODE	Jorm, 1996[188]	Fair	AU	144 NR	POW/veteran	72.9	0	NR	NR NR	NR	AUC
Full IQCODE	Jorm, 1996[188]	Fair	AU	144 NR	POW/veteran	72.9	0	NR	NR NR	NR	AUC
Full IQCODE (Spanish)	Cruz-Orduna, 2011[160]	Fair	ES	160 160	Cognition-related complaint PC	72.4	70	88.8% ≤primary school	9.4 46.9	3.31/3.35	Se, Sp, PPV, NPV, AUC
Full IQCODE	Tokuhara, 2006[195]	Fair	US	299 230	≥65 y Japanese/Okinawan PC	74.2	66	12.2	7 10	3.3	Se, Sp, PPV, NPV, AUC

Abbreviations: AU = Australia; AUC = area under the curve; ES = Spain; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; Se = sensitivity; Sp = specificity.

Table 11. Summary Table: Effectiveness of AChEIs and Memantine (Key Question 4)

Author, Year USPSTF Quality Rating	Daily Dosage (mg)	N randomized	Location	Mean Age (y)	% Female	% Non-white	% Institutionalized or Assisted Living	Mean MMSE Score (MMSE Inclusion Criteria)	Condition	Months to Followup	% Followup	Cognitive Function Outcomes	Global Function Outcomes	Physical Function Outcomes
Donepezil														
Doody, 2009[208,277] Fair	5-10	821	US	70	46	13	NR	27.5 (24-28)	MCI	11	61	↑	↔	NR
Mori, 2012[214] Fair	3-10	140	JP	79	66	100	NR	19.6 (10-26)	DLB	3	88	↑	↑	NR
Requena, 2004[215,440] Fair	5-10	86	ES	77	71	NR	NR	20.8 (NR)	AD	24	96.5	↔	NA	NA
Raina, 2008[110] Good	1-10*	6506	Multi	67-86*	35-82*	1-8*	NR	11.8-27.4* (NR)	VaD, AD, MCI*	3-36*	26-100*	↑	↑	↔
Galantamine														
Auchus, 2007[216] GAL-INT-26 Study Fair	16-24	788	Multi	72	36	8	NR	20.3 (10-26)	VaD	6	80.5	↔	NA	↔
Rockwood, 2006[217, 441-443] VISTA Fair	16-24	130	CA	77	63	NR	0	20.3 (10-25)	AD	4	84	↑	↑	↑
Raina, 2008[110] Good	4-36*	5090	Multi	71-77*	0-64*	0-8*	NR	17.8-20.5* (NR)	VaD, AD, MCI*	1-6*	53-84*	↑	↑	↔
Rivastigmine														
Ballard, 2008[218] VantagE Study Fair	3-12	710	Multi	73	38	18	NR	19.2 (10-24)	VaD	6	80.6	↑	↔	↔
Feldman, 2007[219] Study 304 Fair	2-12	678	Multi	71	59	NR	0	18.6 (10-26)	AD	6	82	↑	↑	↔
Mok, 2007[220] Fair	6	40	HK	75	60	100	NR	13.2 (3-24)	VaD	6	98	↑	↑	↑
Winblad, 2007[221,280, 444-449] IDEAL Study Fair	9.5-17.4 (patch); 12 capsule	1195	Multi	74	67	25	2.6	16.5 (10-20)	AD	6	81.2	↑	↔	↔
Raina, 2008[110] Good	1-12*	2206	Multi	69-84*	44-80*	5*	NR	11.4-20.4* (NR)	AD, DLB*	3-12*	75-100*	↑	↑	↔
Tacrine														
Raina, 2008[110] Good	20-160*	994	Multi	68-75*	46-87*	NR	NR	16.2-18.5* (NR)	AD	3-9*	42-92*	↑	↑	↑
Memantine														
Bakchine, 2008[224] Good	20	470	Multi	74	63	0	NR	18.7 (11-23)	AD	6	87	↔	↑	NR
Ferris, 2007[225] Fair	20	60	US	67	65	10	NR	28.8 (>26)	MCI	3	90	↔	↔	↔
Porsteinsson, 2008[226] MEM-MD-12 Study	20	433	US	75	52	NR	0	16.8 (10-22)	AD	6	89	NR	NR	NR

Table 11. Summary Table: Effectiveness of AChEIs and Memantine (Key Question 4)

Author, Year USPSTF Quality Rating	Daily Dosage (mg)	N randomized	Location	Mean Age (y)	% Female	% Non-white	% Institutionalized or Assisted Living	Mean MMSE Score (MMSE Inclusion Criteria)	Condition	Months to Followup	% Followup	Cognitive Function Outcomes	Global Function Outcomes	Physical Function Outcomes
Good														
Saxton, 2012[222] MEM-MD-71 Good	10	265	Multi	75	58	9	0	15.8 (10-19)	AD	3	95	NR	↑	NR
Wilkinson, 2012[223] Fair	20	278	Multi	74	57	<1	0	16.9 (12-20)	AD	12	78	↔	NR	NR
Raina, 2008[110] Good	5-20*	1959	Multi	76-78*	47-67*	0-6*	NR	7.9-17.6* (NR)	VaD, AD*	6	72-98*	↔	↔	↔

* Range in mean or item reported for each individual study included in Raina 2008.
↑ Statistically significantly favored the intervention.
↔ No statistically significant difference between the intervention and control.

Abbreviations: AChEI = acetylcholinesterase inhibitor; AD = Alzheimer's disease; CA = Canada; DLB = dementia with Lewy bodies; ES = Spain; GAL-INT = galantamine international; HK = Hong Kong; IDEAL =Investigation of transDermal Exelon in Alzheimer's disease; JP = Japan; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; Multi = multiple countries; NR = not reported; USPSTF = U.S. Preventive Services Task Force; VaD = vascular dementia; VISTA = Video-Imaging Synthesis of Treated Alzheimer's Disease.

Table 12. Summary Table: Harms of AChEIs and Memantine (Key Question 5)

Design	Author, Year USPSTF Quality Rating	Daily Dosage (mg)	N	Location	Mean Age (y)	% Female	Mean MMSE Score	Months to Followup	Harm Outcomes
Donepezil									
Trials	Raina, 2008[110] Good	1-10†	6506	NR	67-86†	35-82†	11.8-27.4†	3-36†	Total AE: NR by Raina Withdrawals due to AE (reported in 17/21 trials) Drug: 14% Placebo: 7% Serious AE (reported in 12/21 trials) Drug: 12% Placebo: 11%
	Burns, 2007[α278]	5-10	579	Multi	71	55	20.1	22¥	Total AE Drug: 85% Discontinuation due to AE Drug: 15% Serious AE Drug: 7%
	Wilkinson, 2010[α279]	5-10	885	Multi	75	59	22.0	12	Total AE: NR Discontinuation due to AE Drug: 12% Serious AE: NR
	Doody, 2009[208;277] Fair	5-10	821	US	70	46	27.5	11	Total AE Drug: 81% Placebo: 69% Withdrawals due to AE Drug: 18% Placebo: 8% Serious AE Drug: 12% Placebo: 11%
	Doody, 2009[208;277]	5-10	145	US	73	46	NR	17	Total AE Drug: 57% Placebo: 62% Withdrawals due to AE Drug: 10% Placebo: 22% Serious AE Drug: 4% Placebo: 3%
	Boada-Rovira, 2004[286] Fair	5-10	1113	Multi	71	60	18.7	3	Total AE Drug: 45% Discontinuation due to AE Drug: 5.3% Serious AE: NR
	Mori, 2012[214] Fair	3-10	140	JP	79	66	19.6	3	Total AE Drug: 79% Placebo: 71% Withdrawals due to AE Drug: 2% Placebo 12% Serious AE Drug: 8% Placebo 6%

Table 12. Summary Table: Harms of AChEIs and Memantine (Key Question 5)

Design	Author, Year USPSTF Quality Rating	Daily Dosage (mg)	N	Location	Mean Age (y)	% Female	Mean MMSE Score	Months to Followup	Harm Outcomes
	Relkin, 2008[287] Fair	5-10	1035	US	75	60	19.8‡	3	Total AE Drug: 70%††† Discontinuation due to AE Drug: 6% Serious AE Drug: 9%‡‡‡
Obs	Babai, 2010[288] Fair−	NR	222	FR	81	70	NR	NR	Most commonly (voluntary) reported serious AE (to French pharmacovigilence system): bradycardia (10%), weakness (5%), convulsions (4%)‡‡
	Dunn, 2000[450] Fair−	5-10	1762	UK	73	58	NR	6	Most commonly (voluntary) reported AE (UK surveillance questionnaire to prescribers): nausea/ vomiting (16 per 1000 patient-months of rx), diarrhea (16 per 1000 patient-months of rx), and malaise (7 per 1000 patient-months of rx)
	Hernandez, 2009[290] Good	NR	2888	US	74	4	NR	29	Bradycardia†† Drug: 57% Control: 52% Adjusted HR, 1.2 (95% CI, 1.1 to 1.3)
	Park-Wyllie, 2009[291] Fair+	NR	627	CA	83	51	NR	9	Bradycardia-related hospital admission Drug: 86% Control: 75% Adjusted OR, 2.1 (95% CI, 1.3 to 3.5)
Galantamine									
Trials	Raina, 2008[110] Good	4-36†	5090	NR	71-76.8†	0-64†	17.8-20.5†	1-6†	Total AE: NR by Raina Withdrawals due to AE (reported in 8/10 trials) Drug: 18% Placebo: 7% Serious AE (reported in 6/10 trials) Drug: 8% Placebo: 8%
	Auchus, 2007[216] GAL-INT-26 Study Fair+	16-24	788	Multi	72.3	36	20.3	6	Total AE Drug: 76% Placebo: 71% Discontinued due to AE Drug: 14% Placebo: 7% Serious AE Drug: 20% Placebo: 18%
	Rockwood, 2006[217,441-443] VISTA Fair	16-24	130	CA	77.4	63	20.3	4	Total AE Drug: 84% Placebo: 62% Withdrawal due to AE Drug: 8% Placebo: 3% Serious AE Drug: 8% Placebo: 15%
	Rockwood, 2006[217,441-443]	16-24	130	CA	77.4	63	20.3	8	Total AE- NR Withdrawal due to AE Drug: 13% Placebo: 11% Serious AE Drug: 14% Placebo: 14%

Table 12. Summary Table: Harms of AChEIs and Memantine (Key Question 5)

Design	Author, Year USPSTF Quality Rating	Daily Dosage (mg)	N	Location	Mean Age (y)	% Female	Mean MMSE Score	Months to Followup	Harm Outcomes
	Aronson, 2009[451]	16-24	838	Multi	77.0	64	17.7	5	Total AE Drug: 36% Placebo: 25% Discontinuation due to AE- NR Serious AE Drug: 2% Placebo: 1%
Obs	Hernandez, 2009[290] Good	NR	324	US	74	4	NR	29	Bradycardia†† Drug: 43% Control: 52% Adjusted HR, 1.0 (95% CI, 0.76 to 1.3)
Rivastigmine									
Trials	Raina, 2008[110] Good	1-12†	2206	NR	69.4-83.8†	44-80†	11.4-20.4†	3-12†	Total AE: NR by Raina Withdrawals due to AE (reported in 7/9 trials) Drug: 22% Placebo: 6% Serious AE (reported in 4/9 trials) Drug: 14% Placebo: 12%
	Winblad, 2007[221,280,444-449] IDEAL Study Fair	9.5-17.4 (patch); 12 (capsule)	1195	Multi	73.6	67	16.5	6	Total AE Drug: 60% Placebo: 46% Discontinuation due to AE Drug: 8% Placebo: 5% Serious AE: NR
	Winblad, 2007[221,280,444-449]	9.5-17.4 (patch); 12 (capsule)	1195	Multi	73.6	67	16.5	12	Total AE Drug: 55% Placebo: 63% Discontinuation due to AE: NR Serious AE: NR
	Ballard, 2008[218] VantagE Study Fair+	3-12	710	Multi	72.8	38	19.2	6	Total AE: NR Withdrawal due to AE Drug: 13% Placebo: 6% Serious AE Drug: 15% Placebo: 11%
	Feldman, 2007[219] Study 304 Fair+	2-12	678	Multi	71.4	59	18.6	6	Total AE Drug: 91% Placebo: 76% Withdrawal due to AE Drug: 14% Placebo: 9% Serious AE Drug: 18% Placebo: 15%
	Mok, 2007[220] Fair	6	40	HK	74.9	60	13.2	6	Total AE Drug: 60% Placebo: 50% Withdrawal due to AE Drug: 30% Placebo: 15% Serious AE: NR
Obs	Hernandez, 2009[290] Good	NR	218	US	74	4	NR	29	Bradycardia†† Drug: 87% Control: 52% Adjusted HR, 1.6 (95% CI, 1.2 to 2.0)

Table 12. Summary Table: Harms of AChEIs and Memantine (Key Question 5)

Design	Author, Year USPSTF Quality Rating	Daily Dosage (mg)	N	Location	Mean Age (y)	% Female	Mean MMSE Score	Months to Followup	Harm Outcomes
Tacrine									
Trials	Raina, 2008[110] Good	20-160†	994	NR	68-75†	46-87†	16.2-18.5†	3-9†	Total AE: NR by Raina Withdrawals due to AE (reported in 4/6 trials) Drug: 44% Placebo: 11% Serious AE (reported in 0/6 trials)
Memantine									
Trials	Raina, 2008[110] Good	5-20†	1959	NR	76-78†	47-67†	7.9-17.6†	6	Total AE: NR by Raina Withdrawals due to AE (reported in 5/5 trials) Drug: 10% Placebo: 10% Serious AE (reported in 4/5 trials) Drug: 14% Placebo: 14%
	Ott, 2007[α281] MEM-MD-11AB	20	314	US	77	60	17.3	12	Total AE Drug: 75% Placebo: 75% Withdrawal due to AE Drug: 7% Placebo: 6% Serious AE Drug: 10% Placebo: 12%
	Bakchine, 2008[224] Good	20	470	Multi	74	63	18.7	6	Total AE Drug: 56% Placebo: 53% Withdrawal due to AE Drug: 9% Placebo: 4% Serious AE Drug: 0% Placebo: 0%
	Ferris, 2007[225] Fair−	20	60	US	67	65	28.8	3	Total AE: NR Withdrawal due to AE: NR Serious AE Drug: 0% Placebo: 0%
	Porsteinsson, 2008[226] MEM-MD-12 Study Good	20	433	US	75.4	52	16.8	6	Total AE: NR Withdrawal due to AE Drug: 6% Placebo: 8% Serious AE Drug: 12% Placebo: 14%
	Saxton, 2012[222] MEM-MD-71 Good	20	265	Multi	75	58	15.8	3	Total AE (treatment emergent) Drug: 48.9% Placebo: 49.6% Withdrawals due to AE Drug: 2% Placebo: 3% Serious AE Drug: 3% Placebo: 10.1%
	Wilkinson, 2012[223] Fair	20	278	Multi	74	57	16.9	12	Total AE: NR Withdrawals due to AE Drug: 11% Placebo: 8% Serious AE Drug: 13% Placebo: 14%

Table 12. Summary Table: Harms of AChEIs and Memantine (Key Question 5)

Design	Author, Year USPSTF Quality Rating	Daily Dosage (mg)	N	Location	Mean Age (y)	% Female	Mean MMSE Score	Months to Followup	Harm Outcomes
Obs	Babai, 2010[288] Fair−	NR	95	FR	81	61	NR	NR	Most commonly reported AE: bradycardia (7%), weakness (6%), convulsions (3%)‡‡
	Forstl, 2011[292] Fair	20	4305	Multi	76	87	17.1	6	Total AE Drug: 6% Withdrawal due to AE Drug: 15% Serious AE: NR
	Vidal, 2008[293] Fair	NR	5283	FR	81	69	NR	20	Total AE: NR Withdrawal due to AE Drug: 40% Serious AE: NR
Mixed: Any AChEI and/or Memantine									
Obs	Froelich, 2009[294] Fair−	NR (T, D, R, G, M)	2288	Multi	77*	63	19.0*	24	Total AE Drug: 41%*** Discontinuation due to AE: NR Serious AE Drug: 18%
	Fosbol, 2012[299] Fair	D, G, R, M, or mixed	76233	Multi	81	70	NR	12	Cardiovascular safety profiles of AChEI and memantine did not differ in the Medicare population. Higher risk of MI and cardiac death in persons taking memantine in the Danish cohort likely attributable to selection of sicker population.
	Pariente, 2010[296] Fair−	NR (D, R, G)	773	FR	80*	65	NR	NR	Most commonly (voluntary) reported serious AE (to French pharmacovigilence system): CNS disorders (19%), heart rate/rhythm disorders (16%), GI disorders (14%)‡‡
	Raschetti, 2005[295] Fair	5-10 (D) NR (R, G)	2853	IT	76	67	NR	9	Total AE Drug: 14% Discontinuation due to AE Drug: 5% Serious AE Drug: 18%
	Stephenson, 2012[297] Fair	NR (D, G, R)	14332	CA	82	54	NR	12	In persons with COPD and dementia, no difference in COPD exacerbations, ED visits, hospitalizations, or ICU admissions in people taking AChEI vs. people not taking this class of medication.
	Van Der Putt, 2006[452] Fair	NR (T, D, R, G)	939	UK	80	61	NR	NR	Total AE: NR Discontinuation due to AE Drug: 17% Serious AE: NR

Table 12. Summary Table: Harms of AChEIs and Memantine (Key Question 5)

Design	Author, Year USPSTF Quality Rating	Daily Dosage (mg)	N	Location	Mean Age (y)	% Female	Mean MMSE Score	Months to Followup	Harm Outcomes
	Gill, 2009[298] Good	NR (D, R, G)	81302	CA	80	61	NR	12	Hospitalizations due to: Bradycardia Drug: 7/1000 p-y Control: 4/1000 p-y Adjusted HR, 1.7 (95% CI, 1.3 to 2.2) Hip fracture Drug: 22/1000 p-y Control: 20/1000 p-y Adjusted HR, 1.2 (95% CI, 1.0 to 1.3) Syncope Drug: 32/1000 p-y Control: 19/1000 p-y Adjusted HR, 1.8 (95% CI, 1.6 to 2.0) Pacemaker Drug: 5/1000 p-y Control: 3/1000 p-y Adjusted HR, 1.5 (95% CI, 1.1 to 2.0)
	Hernandez, 2009[290] Good	NR (D, R, G)	3430	US	74	4	NR	29	Bradycardia†† Drug: 57% Control: 52% Adjusted HR, 1.2 (95% CI, 1.1 to 1.3) AE secondary to bradycardia[β] Fall adjusted HR, 2.6 (95% CI, 1.9 to 3.5) Fracture adjusted HR, 0.8 (95% CI, 0.4 to 1.4) Syncope adjusted HR, 3.7 (95% CI, 2.5 to 5.5) Pacemaker, 0.7% vs. 0.2%

† Range in mean or item reported for each individual study included in Raina 2008.
¥ Mean followup time (ranged from 8-46 months).
* Median.
‡ Standardized MMSE.
α OLE to an RCT included in Raina.
** Three OLEs of RCTs included in Raina and three additional open-label studies.
†† ICD-9 code or at least one recorded HR <60.
‡‡ No denominator, so these percentages represent relative frequency of AEs of total reported AEs.
β Drug with bradycardia vs. control without bradycardia.
*** 12% possibly or likely drug related.
††† 44% reported as "related."
‡‡‡ 3% reported as "related."

Abbreviations: AChEI = acetylcholinesterase inhibitor; AD = Alzheimer's disease; AE = adverse event; CA = Canada; DE = Germany; ES = Spain; FR = France; G = galantamine; GAL-INT = galantamine international; HK = Hong Kong; IDEAL = Investigation of transDermal Exelon in Alzheimer's disease; IT = Italy; JP = Japan; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; Multi = multiple countries; NA = not applicable; NR = not reported; Obs = observational; OLE = open-label extension; R = rivastigmine; RCT = randomized, controlled trial; USPSTF = U.S. Preventive Services Task Force; VaD = vascular dementia; VISTA = Video-Imaging Synthesis of Treated Alzheimer's Disease.

Table 13. Summary Table: Effectiveness and Harms of Other Medications (Key Questions 4 and 5)

Author, Year USPSTF Quality Rating	Medication, Daily Dosage	N Randomized	Location	Mean Age (y)	% Female	Mean MMSE Score	Months to Followup	Cognitive Outcomes	Harms Outcomes	Other Outcomes
Vascular Medications										
AD2000[305] Fair	ASA, 75 mg	310	UK	75 (median)	62.9	19	36	↔	Total AE ↑ Severe AE ↑‡‡ Nonadherence (due to AE) ↑††	Physical function ↔ Neuropsychiatric disturbances ↔ Caregiver burden ↔
Clarke, 2003[300] Fair	Aspirin, 81 mg	149	UK	NR (median 75)	NR	21.0‡	3	↔	NR	Physical function ↔
Feldman, 2010[306] Jones, 2008[453] LEADe study Fair	Atorvastatin, 80 mg	640	US	73.6	52.0	21.9	18	↔	Total AE ↑¥ Severe AE ↔ Nonadherence (due to AE) ↑	Physical function ↔ Neuropsychiatric disturbances ↔
Sano, 2011[307] Fair	Simvastatin, 40 mg	406	US	74.6	59.4	20.4	18	↔	Total AE ↔ Severe AE ↔ Nonadherence (due to AE) ↔	Physical function ↔ Neuropsychiatric disturbances ↔ Caregiver burden ↔
Simons, 2002[308] Fair	Simvastatin, 80 mg	44	DE	68.2	55.0	17.5	6	↔	Total AE NR Severe AE NR Nonadherence (due to AE) ↔	None
Sparks, 2005[309] Sparks, 2006[454] Sparks, 2006[455] ADCLT trial Fair	Atorvastatin, 80 mg	63	US	78.5	36.5	20.8	12	↔	NR	Physical function ↔ Depression ↑ Neuropsychiatric disturbances ↔ Caregiver burden ↔
NSAIDs										
Pasqualetti, 2009[310] Fair	Ibuprofen, 800 mg	132	IT	73.9	63.0	20.0	18	↔	Total AE NR Severe AE NR Nonadherence (due to AE) ↔	Physical function ↔ Depression ↔ Neuropsychiatric disturbances ↔ Caregiver burden ↔
Aisen, 2003[311] Fair	Naproxen, 220 mg	351	US	73.9	53.0	20.9	12	↔	Total AE NR Severe AE ↔ Nonadherence (due to AE) ↔	Physical function ↔ HRQL ↔ Neuropsychiatric disturbances ↔
de Jong, 2008[312] Fair	Indomethacin, 100 mg	51	NL	72.5	65.0	19.6	12	↔	Total AE NR Severe AE ↔ Nonadherence (due to AE) ↔	Physical function ↔ Neuropsychiatric disturbances ↔ Caregiver burden ↔
Soininen, 2007[313] Fair	Celecoxib, 40 mg	425	Multi‡	73.6	54.8	19.7	12	↔	Total AE ↔ Severe AE ↔ Nonadherence (due to AE) ↔	Physical function ↔ HRQL ↔ Depression ↔

Table 13. Summary Table: Effectiveness and Harms of Other Medications (Key Questions 4 and 5)

Author, Year USPSTF Quality Rating	Medication, Daily Dosage	N Randomized	Location	Mean Age (y)	% Female	Mean MMSE Score	Months to Followup	Cognitive Outcomes	Harms Outcomes	Other Outcomes
Gonadal steroids										
Henderson, 2000[315] Fair	Estrogen, 1.25 mg	42	US	77.5	100	19.5	4	↔	NR	Physical function ↔ Depression ↔
Lu, 2006[318] Fair-	Testosterone, 75 mg	18	US	69.8	0	22.0	6	↔	Total AE NR Severe AE NR Nonadherence (due to AE) ↔	HRQL ↔ Depression ↔ Neuropsychiatric disturbances ↔
Mulnard, 2000[316] Fair	Estrogen, 0.625 mg or 1.25 mg	120	US	75.1	100	20.7	12	↔	Total AE NR Severe AE NR Nonadherence (due to AE) ↔	Physical function ↔ Depression ↔
Valen-Sendstad, 2010[317] Fair	Progesterone, 0.5 mg + estrogen, 1 mg	65	NO	81.0	100	21.9	12	↔	Total AE ↔ Severe AE ↔ Nonadherence (due to AE) NR	Physical function ↔ Depression ↔
Wang, 2000[314] Fair	Estrogen, 1.25 mg	50	TW	71.8	100	16.2	3	↔	Total AE ↑ Severe AE NR Nonadherence (due to AE) ↔	Depression ↔
Vitamins and supplements										
Aisen, 2008[321] Good	Folic acid, 5 mg + vitamin B12, 1 mg + vitamin B6, 25 mg	409	US	76.3	56.0	21.0	18	↔	Total AE ↔ Severe AE ↔ Nonadherence (due to AE) NR	Physical function ↔ Depression ↔ Neuropsychiatric disturbances ↔
Clarke, 2003[300] Fair	Folic acid, 2 mg + vitamin B12, 1 mg	149	UK	NR (median 75)	NR	21.0‡	3	↔	NR	Physical function ↔
Clarke, 2003[300] Fair	Vitamin E, 500 mg + vitamin C, 200 mg	149	UK	NR (median 75)	NR	21.0‡	3	↔	NR	Physical function ↔
Connelly, 2008[456] Fair	Folic acid, 1 mg**	57	UK	76.3	71.0	23.5	6	↔	NR	Physical function ↑
de Jager, 2012[301] VITACOG Fair	Folic acid, 0.8 mg + cyano-cobalamin, 0.5 mg + pyridoxine HCl, 20 mg	271	UK	77	64	NR	24	↔	Total AE ↔ Severe AE NR Nonadherence (due to AE) NR	Depression ↔
Freund-Lund, 2006[319] Freund-Lund, 2008[457] Fair	DHA, 430 mg + EPA, 150 mg + vitamin E, 4 mg	204	SE	74.0	54.0	23.4	6	↔	NR	Physical function ↔ Depression ↔ Neuropsychiatric disturbances ↔ Caregiver burden ↔
Kwok, 2011[458] Fair	Vitamin B12, 1 mg + folic acid, 5 mg	140	HK	78.2	64.0	16.6	24	↔	NR	Depression ↔ Neuropsychiatric disturbances ↔

Table 13. Summary Table: Effectiveness and Harms of Other Medications (Key Questions 4 and 5)

Author, Year USPSTF Quality Rating	Medication, Daily Dosage	N Randomized	Location	Mean Age (y)	% Female	Mean MMSE Score	Months to Followup	Cognitive Outcomes	Harms Outcomes	Other Outcomes
Sano, 1997[320] Good	Vitamin E, 1000 IU	169	US	73.4	65.7	12.3	24	↔	Total AE NR Severe AE NR Nonadherence (due to AE) NR	Physical function ↔ Neuropsychiatric disturbances ↔
Sinn, 2012[302] Fair	DHA, 1.55 g + EPA, 0.4 g EPA, 1.67 g + DHA, 0.16 g	54	AU	74	32	27.2	6	↔	Total AE NR Severe AE NR Nonadherence (due to AE) ↔	Depression ↑ HRQL ↔
Quinn, 2010[459] Fair	DHA, 2 g	402	US	76	52.2	20.7	18	↔	Total AE ↔ Severe AE ↔ Nonadherence (due to AE) ↔	Physical function ↔ Neuropsychiatric disturbances ↔
Sun, 2007[460] Fair	Vitamin B12, 0.5 mg + multivitamin†	89	JP	75.0	49.0	18.7	6	↔	Total AE ↔ Severe AE ↔ Nonadherence (due to AE) ↔	Physical function ↔
van Uffelen, 2008[303] van Uffelen, 2007[461] van Uffelen, 2005[462] Fair	Folic acid, 5 mg + vitamin B12, 0.4 mg + vitamin B6, 50 mg	179	NL	75.0	44.0	29.0	12	↔	Total AE NR Severe AE NR Nonadherence (due to AE) ↔	HRQL ↔
Yurko-Mauro, 2010[304] Good	DHA, 900 mg	485	US	70.0	57.9	28.2	6	↔	Total AE ↔ Severe AE ↔ Nonadherence (due to AE) ↔	Physical function ↔ Depression ↔

‡ Median.
† Multivitamin contained folic acid, pyridoxine HCl, ferrous (60 mg), nicotinamind (10 mg), calcium carbonate (250 mg), riboflavin (2 mg), thiamine mononitrate (3 mg), calcium panthothenate (1 mg), ascorbic acid (100 mcg), iodine (100 mcg), copper (150 mcg), vitamin B12 (3 mcg), vitamin A (4,000 IU), and vitamin D3 (400 IU).
** All patients received AChEIs.
¥ Not significant for total AEs, but significant for treatment-related total AEs.
†† Overall nonadherence, not necessarily due to AE.
‡‡ Serious bleeding events.
↔ No statistically significant difference between the intervention and control groups.

Abbreviations: AD = Alzheimer's disease; ADCLT = Alzheimer's disease cholesterol-lowering treatment; AE = adverse events ; ASA = acetylsalicylic acid; AU = Australia; DE = Germany; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HK = Hong Kong; HRQL = health-related quality of life; IT = Italy; JP = Japan; LEADe = Lipitor's Effect in Alzheimer's Dementia; multi = multiple countries; NL = The Netherlands; NO = Norway; NR = not reported; NSAIDs = nonsteroidal anti-inflammatory drugs; MMSE = Mini Mental State Examination; SE = Sweden; TW = Taiwan; UK = United Kingdom; USPSTF = U.S. Preventive Services Task Force.

Table 14. Summary Table: Effectiveness of Caregiver Interventions (Key Question 4)

Author, Year USPSTF Quality Rating	N Randomized	Location	% Spouse	Minimum Amount of Caregiving	Mean MMSE Score	Months to Followup	Caregiver Burden Outcome	Caregiver Depression Outcome	Patient Institutionalization Outcome	Other Outcomes
Group-Based Psychoeducation										
REACH II, 2006[352] Fair	642	US	43.2	4 h/d	12.9	6	↑	↑	↔	Caregiver self-related health (↑); patient symptoms (↑)
Brodaty, 1989[361] Fair	101	AU	92.7	NR	NR*	18	NR	NR	↑	Caregiver distress (↑); patient mortality (↔)
REACH-Birmingham, 2003[330] Fair	140	US	50	4 h/d	13.1	6	↑	↔	NR	Caregiver anxiety (↔); patient behavior (↔)
Chu, 2011[353] Fair	85	TW	32.2	4 h/d	NR	4	↔	↑	NR	
Coon, 2003[374] Fair	169	US	57	NR	14.2	7	NR	↑	NR	
REACH-Palo Alto, 2003 (IG1)[325] Fair	257	US	NR	4 h/d	13.7	6	↔	↔	NR	
De Rotrou, 2011[463] Fair	157	FR	57	4 h/wk	NR	6	↔	↔	↔	Patient cognitive (↔), physical (↔), behavior (↔)
Gallagher-Thompson, 2008[367] Fair+	184	US	38	8 h/d	14	6	↑	↑	NR	Caregiver stress (↑)
Hebert, 1994[362] Fair-	121	CA	68	Wkly	14.6	8	↔	NR	↔	Caregiver symptoms (↔)
Hepburn, 2001[371] Fair	117	US	66	NR	NR	5	↑	↑	NR	Caregiver distress (↑)
Hepburn, 2005[146] Fair-	223	US	66	NR	17.7	12	↔	NR	NR	Patient cognitive (↔), physical (↔), behavior (↔)
Kurz, 2010[358] Fair	292	AT, CH, DE	58	Daily	13.9	15	NR	↔	↔	Caregiver emotional role (↑), social role (↔), mental health (↔)
Losada, 2010[377] Fair	167	ES	35	1 h/d	NR	3	NR	↑	NR	Caregiver dysfunctional thoughts (↑)
Ostwald, 1999[372] Fair	117	US	NR	NR	NR	5	↑	↔	NR	Patient cognitive function (↔)
Ulstein, 2007[360] Fair	180	NO	70	Wkly	20.8	12	↔	NR	↔	Patient mortality (↔)
Waldorff, 2012[368] Good	330	DK	65	Wkly	24.1	12	NR	↑	NR	Caregiver HRQL (↔); patient cognitive function (↔), physical (↔), HRQL (↔), depression (↑)

Table 14. Summary Table: Effectiveness of Caregiver Interventions (Key Question 4)

Author, Year USPSTF Quality Rating	N Randomized	Location	% Spouse	Minimum Amount of Caregiving	Mean MMSE Score	Months to Followup	Caregiver Burden Outcome	Caregiver Depression Outcome	Patient Institutionalization Outcome	Other Outcomes
Individual Psychoeducation										
Chang, 1999[375] Fair	87	US	88.6	NR	NR	3	NR	↑	NR	Caregiver anxiety (↔); patient functioning (↔)
Ducharme, 2011[365] Fair	121	CA	34.2	NR	NR	5	NR	NR	NR	Plan for future treatment needs (↔)
Gitlin, 2001[340] Fair	202	US	25.1	NR	NR	3	↔	NR	NR	Patient problem behaviors (↔), physical function (↔)
REACH-Philadelphia, 2003[332] Fair	255	US	35.3	4 h/d	12.2	6	↔	↔	NR	Caregiver wellbeing (↔); patient ADL (↔), IADL (↔), memory-related behavior (↔), disruptive behavior (↔)
Gitlin, 2008[354] Fair	60	US	61.7	4 h/d	11.6	4	NR	↔	NR	Patient morality (↔), QOL (↔), depression (↔), problem behavior (↔)
Gitlin, 2010 (ACT)[342] Fair	272	US	51	NR	13	6	↑	↑	NR	
Gitlin, 2010 (COPE)[341] Fair	237	US	37.8	8 h/wk	13.4	4	NR	NR	NR	Caregiver well-being (↑); patient IADL (↑), ADL (↔), QOL (↔), agitation (↔)
Graff, 2006[343] Fair	135	NL	58.8	Wkly	19.0	3	NR	↑	↔	Caregiver QOL (↑), distress (↑); patient mortality (↔), function (↑),QOL (↑), depression (↑)
Hebert, 2003[363] Fair	158	CA	61	NR	NR	4	↑	NR	↔	Caregiver psychiatric symptoms (↔), anxiety (↔); patient mortality (↔), behavior (↔)
Hinchliffe, 1995[357,357] Fair	40	UK	70	NR	NR	4	NR	NR	NR	Caregiver distress (↑), mental health diagnosis (↑)
Huang, 2003[366] Fair	59	TW	35.4	NR	13.1	3	NR	NR	NR	Patient behavior (↑)
Marriott, 2000[359] Fair	42	UK	52.4	NR	12.5	12	NR	↑	NR	Caregiver distress (↑); patient cognitive function (↔), ADL (↑), depression (↔)
Martin-Carrasco, 2009[355] Fair	115	ES	54.8	4 h/d	18.7	10	↑	NR	NR	Caregiver distress (↑), functioning (↑)

Table 14. Summary Table: Effectiveness of Caregiver Interventions (Key Question 4)

Author, Year USPSTF Quality Rating	N Randomized	Location	% Spouse	Minimum Amount of Caregiving	Mean MMSE Score	Months to Followup	Caregiver Burden Outcome	Caregiver Depression Outcome	Patient Institutionalization Outcome	Other Outcomes
Martin-Cook, 2005[379] Fair	49	US	91.5	NR	19.4	4	NR	↔	NR	Patient cognitive function (↔)
Roberts, 1999[364] Fair	83	CA	52	NR	NR	12	NR	NR	NR	Caregiver adjustment to patient illness (↔)
Schoenmakers, 2010[376] Fair	62	BE	46	NR	NR	12	NR	↑	NR	Patient hospitalization (↔)
Spijker, 2011[337] Good	301	NL	27.6	2 d/wk	NR	12	NR	NR	↔	
Teri, 2005[145] Fair	95	US	55.3	NR	13.6	6	↑	↑	↔	Patient QOL (↑), memory-related behavior (↑)
Voigt-Radloff, 2011[344] Fair	141	DE	56	2 d/wk	20.4	12	↔	↔	↔	Caregiver function (↔), patient mortality (↔), IADL (↔),QOL (↔), depression (↔)
Williams, 2010[378] Fair	116	US	41	NR	NR	6	NR	↔	NR	Caregiver anxiety (↔), stress (↔)
Wright, 2001[464] Fair	93	US	45	NR	NR	12	↔	↔	↔	Caregiver physical health (↔); patient agitation (↔)
Computer- or Phone-Based Psychoeducation										
Brennan, 1995[338] Fair	102	US	58	NR	NR	12	↔	↔	↔	
Finkel, 2007[339] Fair	46	US	44	4 h/wk	NR	6	↔	↔	NR	Patient mortality (↔), behavior (↔)
REACH-Boston, 2003[333] Fair	100	US	54	4 h/d	11.4	6	↔	↔	NR	Caregiver anxiety (↔)
Family-Based Psychoeducation										
Joling, 2012[334,465] Fair	192	NL	94.3	NR	21.6	12	↔	↔	↔	Caregiver anxiety (↔), function (↔)
Mittleman, 2008[335] Fair	158	AU	NR	NR	20.3	24	NR	↑	↔	Patient mortality (↔)
Psychoeducation + Care/Case Management										
Bass, 2003[345] Fair	182	US	NR	NR	NR	12	NR	↑	NR	Caregiver health deterioration (↔); patient hospitalization (↔), emergency department visits (↔)

Table 14. Summary Table: Effectiveness of Caregiver Interventions (Key Question 4)

Author, Year USPSTF Quality Rating	N Randomized	Location	% Spouse	Minimum Amount of Caregiving	Mean MMSE Score	Months to Followup	Caregiver Burden Outcome	Caregiver Depression Outcome	Patient Institutionalization Outcome	Other Outcomes
Callahan, 2006[346] Fair	153	US	44.5	NR	18.1	18	↑	↑	↔	Caregiver distress (↑); patient mortality (↔), cognitive function (↑), depression (↔)
Chu 2000[347] Fair	78	CA	NR	NR	22.8	18	↑	NR	↔	Patient mortality(↔), cognitive function (↔), depression (↔), behavior (↔)
Eloniemi-Sulkava, 2009[356] Good	125	FI	100	NR	13.8	24	NR	NR	↔	Patient mortality (↔)
Eloniemi-Sulvaka, 2001[348] Fair	100	FI	56	NR	14.8	24	NR	NR	↔	Patient mortality (↔)
Fortinsky, 2009[349] Fair	84	US	45	NR	NR	12	↔	↔	↔	
REACH-Memphis, 2003[332] Fair	245	US	NR	4 h/d	11.1	6	↔	↔	NR	
Jansen 2011[350] Fair	99	NL	40.4	NR	22.3	12	↔	↔	NR	Caregiver function (↔); patient mortality (↔),QOL (↔)
Lam, 2010[351] Fair	102	HK	29.4	NR	17.8	12	↔	NR	↔	Caregiver distress (↔), QOL (↔); patient cognitive function (↔),QOL (↔), depression (↔), neuropsychiatric symptoms (↔)
Vickrey 2006[336] Good	408	US	54.8	NR	NR†	18	NR	NR	NR	Caregiver QOL (↔); patient mortality (↔), hospitalization (↔), emergency department visits (↔), QOL (↑)
Assessment and Treatment Planning										
Logiudice, 1999[329] Fair	50	AU	54	Wkly	17.0	12	↔	NR	↔	Caregiver distress (↔); patient mortality (↔)
Peer Support Only										
Charlesworth, 2008[322] Fair	236	UK	67	20 h/wk	NR	24	NR	↔	↔	Caregiver anxiety (↔),QOL (↔); patient mortality (↔)

Table 14. Summary Table: Effectiveness of Caregiver Interventions (Key Question 4)

Author, Year USPSTF Quality Rating	N Randomized	Location	% Spouse	Minimum Amount of Caregiving	Mean MMSE Score	Months to Followup	Caregiver Burden Outcome	Caregiver Depression Outcome	Patient Institutionalization Outcome	Other Outcomes
REACH-Palo Alto, 2003 (IG2)[325] Fair	257	US	NR	4 h/d	13.7	6	↔	↔	NR	
Pillemer, 2002[323] Fair	147	US	40	NR	NR	6	NR	↔	NR	
Winter, 2006[324] Fair	103	US	40.8	NR	NR	6	↔	↔	NR	
Physical Activity Counseling										
Connell, 2009[326] Fair	157	US	100	NR	NR	12	↔	↔	NR	Caregiver stress (↑)
Hirano, 2011[327] Fair	36	JP	NR	NR	18.3	3	↔	↔	NR	Patient behavior (↔)
King, 2002[328] Fair	100	US	53	10 h/wk	NR	12	↔	↔	NR	Caregiver stress (↔), anxiety (↔); patient behavior (↔)

* Mean CDR, 1.1.
† Dementia severity score, 6.
↑ Statistically significantly favored the intervention.
↔ No statistically significant difference between the intervention and control groups.

Abbreviations: ACT = Advancing Caregiver Training; ADL = activities of daily living; AT = Austria; AU = Australia; BE = Belgium; CA = Canada; CDR = clinical dementia rating; CH = Switzerland; COPE = Care of Persons with Dementia in their Environments; DE = Germany; DK = Denmark; ES = Spain; FI = Finland; FR = France; HK = Hong Kong; IADL = instrumental activities of daily living; IG = intergenerational; JP = Japan; MMSE = Mini-Mental State Examination; NL = The Netherlands; NO = Norway; NR = not reported; QOL = quality of life; REACH = Resources for Enhancing Alzheimer's Caregiver Health; TW = Taiwan; UK = United Kingdom; USPSTF = U.S. Preventive Services Task Force.

Table 15. Summary Table: Effectiveness and Harms of Other Nonpharmacologic Interventions (Key Questions 4 and 5)

Author, Year USPSTF Quality Rating	n Randomized	Location	Mean Age (y)	% Female	Mean MMSE Score	Months to Followup	Cognitive Function Outcome	Physical/ Global Function Outcome	HRQL Outcome	Institutionalization Outcome	Other Outcomes
Cognitive Stimulation											
Chapman, 2004[391] Fair	54	US	76.4	54	20.9	12	↔	↔	↔	↔	Neuropsychiatric disturbances ↔ Caregiver burden ↔
Requena, 2004[215] Requena, 2006[440] Fair	86	ES	77.0	71	20.8	24	↑	NR	NR	NR	Depression ↔
Cognitive Stimulation and Training											
Buschert, 2011[384] Fair	24	DE	71.2	50	27.4	6	↑	NR	↔	NR	Depression ↔
Tsolaki, 2011[386] Fair	196	GR	67.8	72	27.9	6	↑	↑	NR	NR	None
Buschert, 2011[384] Fair	15	DE	75.9	53	24.9	6	↔	NR	↔	NR	Depression ↑
Olazaran, 2004[385] Fair	84	ES	74.4	60	NR	12	↔	↔	NR	NR	Depression ↑ Neuropsychiatric disturbances ↑
Quayhagen, 1995[466]* Fair	95	US	73.6	35	NR	6	↑	NR	NR	NR	None
Cognitive Training											
Kinsella, 2009[380] Fair	54	AU	76.8	57	26.4	4	Memory ↔	NR	↔	NR	None
Rapp, 2002[381] Fair	19	US	74.3	58	27.6	6	NR	NR	NR	NR	None
Troyer, 2008[382] Fair	54	CA	75.4	54	27.9	6	Memory ↔	NR	NR	NR	None
Burgener, 2008[387] Fair	43	US	77.1	47	NR (CDR, 1.2)	5	↔	NR	NR	NR	Depression ↔
Cahn-Weiner, 2003[388] Fair	34	US	76.9	59	24.7	3	Memory ↔	↔	NR	NR	None
Clare, 2010[389] Fair	68	WAL	77.5	59	22.9	6	Memory ↔	NR	↔	NR	Depression ↔
Greenaway, 2012[383] Fair	40	US	73	61	26.8	6	↔	NR	↔	NR	Patient depression ↔ Patient anxiety ↔ Caregiver burden ↑ Caregiver HRQL ↔ Caregiver depression ↑ Caregiver anxiety ↔

Table 15. Summary Table: Effectiveness and Harms of Other Nonpharmacologic Interventions (Key Questions 4 and 5)

Author, Year USPSTF Quality Rating	n Randomized	Location	Mean Age (y)	% Female	Mean MMSE Score	Months to Followup	Cognitive Function Outcome	Physical/ Global Function Outcome	HRQL Outcome	Institutionalization Outcome	Other Outcomes
Schwenk, 2010[390] Fair	61	DE	81.5	64	21.4	3	Other ↔	NR	NR	NR	None
Other											
Kurz, 2012[393] Fair	201	DE	74	44	25.1	6	↔	↔	↔	NR	Patient depression ↔ Patient behavior ↔ Caregiver depression ↔ Caregiver burden ↔
Exercise											
Baker, 2010[396] Fair	33	US	69.6	52	27.4	6	Memory ↔	NR	NR	NR	None
Lam, 2011[394] Fair	389	HK	77.8	76	24.5	5	↔	NR	NR	NR	Depression ↔ Neuropsychiatric disturbances ↔
Lautenschlager, 2008 (FAB)[213] Fair	170	AU	68.7	51	NR	18	↑	NR	↔	NR	Depression ↔ Total AE ↔
Nagamatsu, 2012[397] Fair-	86	CA	74.9	100	26.8	6	Memory ↔	NR	NR	NR	Total AE ↔
Steinberg, 2009[398] Fair	27	US	75.3	70	17.7	3	↔	NR	↔	NR	Depression ↔ Neuropsychiatric disturbances ↔ Caregiver burden ↔ Serious AE ↔
Suzuki, 2012[212] Fair	50	JP	76	46	26.7	12	↑	NR	NR	NR	NR
Teri, 2008[400] Good	153	US	78.0	41	16.7	18	NR	↑	↑	↔	Depression ↔
Tsai, 2012[395] Fair	55	US	79	73	25.5	5	↔	NR	NR	NR	NR
Venturelli, 2010[401] Fair	30	IT	83.7	NR	NR	3	↑	↑	NR	NR	Hospitalization ↔ Total AE ↔
Vreugdenhil, 2012[399] Fair	40	AU	74	60	22.0	4	↑	↑	NR	NR	Patient depression ↔ Caregiver burden ↔
Multidisciplinary Assessment											
Bellantonio, 2008[402] Fair	100	US	82.2	63	14.8	9	NR	NR	NR	↔	Hospitalization ↔ ED visits ↔

Table 15. Summary Table: Effectiveness and Harms of Other Nonpharmacologic Interventions (Key Questions 4 and 5)

Author, Year USPSTF Quality Rating	n Randomized	Location	Mean Age (y)	% Female	Mean MMSE Score	Months to Followup	Cognitive Function Outcome	Physical/ Global Function Outcome	HRQL Outcome	Institutionalization Outcome	Other Outcomes
Meeuwsen, 2012 Good	175	NL	78	61	22.7	12	NR	↔	↔	NR	Patient depression ↔ Patient behavior ↔ Caregiver HRQL ↔ Caregiver depression ↑ Caregiver distress ↔ Caregiver anxiety ↑
Nourhashemi, 2010 (PLASA)[404] Fair	1131	FR	80.2	69	19.7	24	NR	↔	NR	↔	None
Richard, 2009[403] Fair	130	NL	76.5	57	22.3	24	↔	↔	NR	↔	Neuropsychiatric disturbances ↔
Wolfs, 2008[406] Fair	230	NL	77.9	64	20.2	12	↔	↔	↔	NR	Depression ↔ Neuropsychiatric disturbances ↔
Education Only											
Beer, 2011[407] Beer, 2010[467] Fair	351	AU	85.3	76	NR (Median for IG, 10; median for CG, 12)	6	NR	NR	↔	NR	Hospitalization ↔ Neuropsychiatric disturbances ↔ Caregiver burden ↔
Menn, 2012[408] Fair	390	DE	80	68	18.7	24	NA	NA	NA	↔	

↑ Statistically significantly favored the intervention.
↔ No statistically significant difference between the intervention and control groups.

Abbreviations: AU = Australia; CA = Canada; CDR = clinical dementia rating; CG = caregiver; DE = Germany; ES = Spain; FAB = Fitness for the Aging Brain; FR = France; GR = Greece; HK = Hong Kong; HRQL = health-related quality of life; IG = intergenerational; IT = Italy; JP = Japan; MMSE = Mini-Mental State Examination; NA= not abstracted because of poor followup (<60%); NL = The Netherlands; NR = not reported; PLASA = Plan de Soin et d'Aide dans la maladie d'Alzheimer; USPSTF = U.S. Preventive Services Task Force; WAL = Wales.

Table 16. Summary of Evidence

KQ, by Instrument or Treatment	Number, Design	Quality	Applicability	Consistency	Diagnostic Accuracy or Magnitude of Effect (Including Precision)
KQ 1	None	NA	NA	NA	NA
KQ 2 (dementia)	46 Dx accuracy	Fair to good	Wide range of instruments, broad inclusion of older adult populations with a wide range of underlying dementia	Some inconsistencies in estimates of diagnostic performance, unclear if due to differences in study quality, populations, or scoring of instrument	The best-studied instrument is the MMSE, but administration time can be 10 minutes. Other instruments with more limited evidence include the CDT, Mini-Cog, MIS, AMT, SPMSQ, FCSRT, 7MS, TICS, and IQCODE. Each of these tests can have reasonable test performance, but estimates of sensitivity and specificity vary. The AMT, SPMSQ, FCSRT, 7MS, and TICS have very limited evidence in English. Other instruments such as the 6-item screener, VAT, GPCOG, ADL/IADL, Benton's Orientation Test, and Delayed Recall Test, and the Short Concord Informant Dementia Scale for dementia, appear promising, but their test performances have not been reproduced in other primary care–relevant populations.
-CDT	7 Dx accuracy	Fair to good	Wide range of prevalence, unclear optimal scoring/cut-point	Unclear if inconsistency due to difference in population (e.g., education) or scoring methods/cut-points	6 studies (n=2170) Sn, 67-97.9 (95% CI, 39 to 100) Sp, 69-94.2 (95% CI, 54 to 97.1)
-Mini-Cog	4 Dx accuracy	Fair to good	Wide range of prevalence, unclear optimal cut-point	Unclear if inconsistency due to difference in population (e.g., education) or scoring methods/cut-points for CDT	4 studies (n=1208) Sn, 76-100 (95% CI, 54 to 100) Sp, 54-85.2 (95% CI, 43 to 88.4)
-MIS(-T)	5 Dx accuracy	Fair to good	Wide range of prevalence	Two best-quality studies with low sensitivity	5 studies (n=1971) Sn, 43-86 (95% CI, 24 to 96) Sp, 93-97 (95% CI, 56 to 100)
-MSQ or SPMSQ	4 Dx accuracy	Fair	Wide range of prevalence, only one study in English, unclear optimal cut-point	SPMSQ and MSQ performed similarly in 2 studies evaluating both, unclear if inconsistency due to cut-points	4 studies (n=940) Sn, 92.3-100 (95% CI, 29 to 100) Sp, 83.5-100 (95% CI, 76 to 100)
-Verbal fluency	6 Dx accuracy	Fair to good (mostly fair)	Wide range of prevalence	Test performance overlapped regardless of cut-point	For a cut-point of 12 or 13: 3 studies (n=1041) Sn, 37-89.5 (95% CI, 19 to 100) Sp, 62-97 (95% CI, 48 to 99) For a cut-point of 14: 3 studies (n=905) Sn, 57-88 (95% CI, 35 to 100) Sp, 43-94 (95% CI, 33 to 97)
-AMT	4 Dx accuracy	Fair	Wide range of prevalence, only one study in English, and none of the studies conducted in the U.S.	Unclear if inconsistency due to difference in population (language, culture, underlying prevalence)	4 studies (n=863) Sn, 42-100 (95% CI, 16 to 100) Sp, 83-95.4 (95% CI, 76 to 99)

Table 16. Summary of Evidence

KQ, by Instrument or Treatment	Number, Design	Quality	Applicability	Consistency	Diagnostic Accuracy or Magnitude of Effect (Including Precision)
-FCRST	2 Dx accuracy	Fair to good	High prevalence of dementia, only one study in English, unclear optimal cut-point	Only 2 studies, different populations and cut-points	2 studies (n=734) Sn, 86-100 (95% CI, 41 to 100) Sp, 73-87.2 (95% CI, 56 to 96)
-7MS	2 Dx accuracy	Fair	Intermediate prevalence of dementia, only one study in English, unclear optimal cut-point	Only 2 studies, different populations and cut-points	2 studies (n=553) Sn, 100 (95% CI, 71.5 to 100) Sp, 95.1-100 (95% CI, 86.8 to 100)
-TICS	2 Dx accuracy	Fair	Intermediate prevalence of dementia, only one study in English, unclear optimal cut-point	Only 2 studies, different populations and cut-points	2 studies (n=677) Sn, 74-88 (95% CI, 54 to 96) Sp, 86-87 (95% CI, 81 to 91)
-MMSE	25 Dx accuracy	Fair	Wide range of prevalence, wide range of languages	Test performance overlapped regardless of cut-point of 23/24 or 24/25, optimal cut-point for low education is lower	For a cut-point of 23/24, 24/25: 14 studies (n=10,185) Sn, 88.3 (95% CI, 81.3 to 92.9) Sp, 86.2 (95% CI, 81.8 to 89.7)
-IQCODE	5 Dx accuracy	Fair to good (mostly fair)	Intermediate prevalence of dementia, unclear optimal cut-point, cut-point recommended by test developers not supported in evidence	Test performance overlapped for short and full versions, and overlapped for different cut-points	5 studies (n=1108) Sn, 75-87.6 (95% CI, 41 to 100) Sp, 65-91.1 (95% CI, 59 to 100)
-Other instruments	1 Dx accuracy study for each instrument	Fair to good	Cannot comment on applicability because instruments only evaluated in one study, lack of reproducibility in primary care–relevant population	Cannot comment on consistency of findings because instruments only evaluated in one study	6-item screener, VAT, GPCOG, ADL/IADL, Short Concord Informant Dementia Scale, Benton's Orientation Test, and Delayed Recall Test have Sn/Sp >80%
KQ 2 (MCI ± dementia)	27 Dx accuracy	Fair to good	Wide range of instruments, broad inclusion of older adult populations with a wide range of underlying dementia	Inconsistencies in estimates of diagnostic performance; unclear if due to differences in study quality, definitions, diagnostic criteria for MCI, populations, or scoring of instrument	Overall, screening instruments have less evidence to support their use to detect MCI and have much lower sensitivity to detect MCI than dementia. The MoCA, specifically designed to detect MCI, has limited evidence in English. Several instruments, including AD8, SLUMS, FOME, and CAMCI for MCI, appear promising, but their test performance has not been reproduced in other primary care–relevant populations.
-CDT	4 Dx accuracy	Fair	Unclear optimal definition of MCI, and unclear optimal scoring/cut-point	Unclear if inconsistency due to difference in definition of MCI, prevalence of underlying MCI, education level, or scoring/cut-points	4 studies (n=4191) to detect MCI Sn, 40-85 (95% CI, 34.1 to 97) Sp, 44-83 (95% CI, 33 to 87.5)

Table 16. Summary of Evidence

KQ, by Instrument or Treatment	Number, Design	Quality	Applicability	Consistency	Diagnostic Accuracy or Magnitude of Effect (Including Precision)
-Mini-Cog	3 Dx accuracy	Fair to good	Unclear optimal definition of MCI, and unclear optimal scoring of CDT	Unclear if inconsistency due to difference in definition of MCI, prevalence of underlying MCI, or scoring of CDT	1 study (n=91) to detect MCI Sn, 50 (95% CI, 38 to 62) Sp, 73 (95% CI, 42 to 92) 2 studies (n=1001) to detect MCI + dementia Sn, 39-84 (95% CI, 34 to 88.5) Sp, 78-87.9 (95% CI, 73 to 92.8)
-TICS(-M)	3 Dx accuracy	Fair	Unclear optimal definition of MCI, and unclear optimal cut-point	Each study found a different optimal cut-point; unclear if inconsistency due to difference in definition of MCI or differences in population (prevalence, education, language)	For cut-point of 26 or 27: 1 study (n=71) to detect MCI Sn, 17.6 (95% CI, 3.8 to 43.4) Sp, 100 (95% CI, 93.4 to 100) 2 studies (n=497) to detect MCI + dementia Sn, 73-99 (95% CI, 64 to 100) Sp, 46-77 (95% CI, 35 to 82)
-MMSE	15 Dx accuracy	Fair to good	Unclear optimal definition of MCI, and unclear optimal cut-point	Unclear if inconsistency due to difference in definition of MCI, population (prevalence, education, language), or cut-points	For a cut-point of 23 or 24: 3 studies (n=1544) to detect MCI Sn, 72-77 (95% CI, 62.5 to 85) Sp, 70-89 (95% CI, 58 to 98.6) For a cut-point of 27 or 28: 3 studies (n=1235) to detect MCI Sn, 45-60 (95% CI, 36 to 74) Sp, 65-90 (95% CI, 56 to 99) 1 study (n=63) to detect MCI + dementia Sn, 71 (95% CI, 48 to 89) Sp, 90 (95% CI, 77 to 97)
-IQCODE	4 Dx accuracy	Fair	Unclear optimal definition of MCI, and unclear optimal cut-point	Unclear if inconsistency due to difference in definition of MCI, underlying prevalence, or cut-points	1 study (n=441) to detect MCI Sn, 74.8 (95% CI, 67.7 to 80.7) Sp, 69.0 (95% CI, 63.1 to 74.7) 2 studies (n=390) to detect MCI + dementia Sn, 71.1-82.6 (95% CI, 60.6 to NR) Sp, 74.3-83.0 (95% CI, 62.4 to 84.0)
-MoCA	2 Dx accuracy	Fair to good	Unclear optimal cut-point	Unclear if inconsistency due to difference in underlying population characteristics	For cut-point of 25/26: 2 studies (n=554) to detect MCI Sn, 80-100 (95% CI, 56.3 to 100) Sp, 50-76 (95% CI, 41 to 84.9)
-Other instruments	1 Dx accuracy study for each instrument	Fair to good	Cannot comment on applicability because instruments only evaluated in one study, lack of reproducibility in primary care–relevant population	Cannot comment on consistency of findings because instruments only evaluated in one study	AD8, FOME, SLUMS, CAMCI have Sn/Sp >80%

Table 16. Summary of Evidence

KQ, by Instrument or Treatment	Number, Design	Quality	Applicability	Consistency	Diagnostic Accuracy or Magnitude of Effect (Including Precision)
KQ 3	1 Dx accuracy	Fair	Unclear applicability given single study in urban low-income area in mostly black women	Cannot comment on consistency of findings because only one study	No studies directly reported adverse effects from screening, subsequent diagnostic testing, or missed/delayed diagnosis. One study (n=434) reported 48% of older adults who screened positive for cognitive impairment refused to complete a diagnostic workup for dementia.
KQ 4 (dementia and MCI)	1 SER and 130 RCTs	Fair to good	Older adults with mild to moderate dementia (mainly AD) or MCI, underrepresentation of nonwhite populations, some complex interventions not widely available	Within specific types of interventions, generally consistent findings by outcome. Inconsistent reporting of certain important outcomes.	For dementia, AChEIs and memantine can improve global cognitive function in the short-term; on average, these effects are likely not clinically signficant but may be for targeted individuals who we cannot evaluate. Complex interventions aimed at caregivers or dyads can result in small improvement in caregiver burden and depression, but the clinical significance of these small changes is not clear. Evidence of benefits for medications and caregiver interventions are mainly in persons with moderate (as opposed to mild) dementia. Cognitive stimulation ± training can improve global cognitive function, but this is based on a much more limited body of evidence and the very large imprecision around benefit limits meaningful interpretation. For MCI, the body of evidence is much smaller, without substantial reproducibility or consistency of findings of benefit for AChEIs, memantine, or cognitive stimulation.
Pharmacologic interventions	FDA-approved medications: 1 SER (50 RCTs) and 14 RCTs Other medications: 26 RCTs	Fair to good	Older adults with mild to moderate dementia (mainly AD), underrepresentation of nonwhite populations, doses of medications or supplements applicable to common use	Inconsistent by class of medication, but within classes of medications/supplements, findings are consistent for major outcomes. Cannot evaluate inconsistency of other outcomes given sparse reporting.	For dementia, AChEIs and memantine can improve global cognitive function in the short-term, but the clinical significance is unclear; using accepted thresholds of clinical benefit, the average benefit across patients is clinically insignificant. AChEIs can improve scores on a clinically meaningful measure of global function in the short-term. Evidence in people with MCI is sparse, with no benefit on global cognitive function. Other medications evaluated had no benefit on global cognitive or physical function in people with dementia or MCI.

Table 16. Summary of Evidence

KQ, by Instrument or Treatment	Number, Design	Quality	Applicability	Consistency	Diagnostic Accuracy or Magnitude of Effect (Including Precision)
AChEIs	1 SER (45 RCTs) and 9 RCTs	Fair to good	Older adults with mild to moderate dementia (few trials in MCI), mostly AD (few trials in VaD); populations primarily from North America and western Europe; doses of medications applicable to common use	Consistent findings in global cognitive function. Generally consistent findings of benefit in global function outcomes. Inconsistent findings of benefit in physical function; cannot evaluate inconsistency given sparse reporting.	Donepezil (k=24; n=7553), galantamine (k=12; n=6008), and rivastigmine (k=12; n=4829) have statistically significant benefits on global cognitive function in the short-term (approximately 1 to 3 points change on the ADAS-cog). In a small subset of trials, donepezil, galantamine, and rivastigmine have a small benefit on global function, using a clinically meaningful scale, in the short-term. Physical function was only reported in half the trials and showed mixed results. Only 4 trials (3 for donepezil, 1 for galantamine) in MCI. While small statistically significant benefits were demonstrated for donepezil, 2 trials of donepezil showed no difference in progression of MCI to dementia at 3 years.
Memantine	1 SER (5 RCTs) and 5 RCTs	Fair to good	Older adults with mild to moderate dementia, mostly AD (2 trials in VaD); populations from North America and western Europe; doses of medications applicable to common use	Consistent findings in global cognitive function. Inconsistent findings of benefit in global and physical function; cannot determine if differences in population or study characteristics explain inconsistencies	Statistically significant but clinically marginal benefits in cognitive function in the short-term (k=9; n=3323). Mixed benefit in global function (k=7; n=1880) and physical function (k=5; n=1962). Benefits appear to be limited to persons with moderate AD.
Aspirin	2 RCTs	Fair	Older adults with mild to moderate dementia or MCI, mainly AD; populations from U.S. and western Europe; low-dose aspirin	Consistent finding of no benefit	No benefit in global cognitive or physical function for low-dose ASA (n=459)
Statins	4 RCTs	Fair	Older adults with mild to moderate dementia, mainly AD; populations from U.S. and western Europe; doses of medications applicable to common use	Consistent finding of no benefit	No benefit in global cognitive function, physical function, or neuropsychiatric symptoms for simvastatin or atorvastatin (n=1153)
NSAIDs	4 RCTs	Fair	Older adults with mild to moderate dementia, populations from U.S. and western Europe; doses of medications applicable to common use	Consistent finding of no benefit despite type of NSAID	No benefit in global cognitive or physical function for ibuprofen, naproxen, indomethacin, or celecoxib (n=959). Other outcomes sparsely reported.

Table 16. Summary of Evidence

KQ, by Instrument or Treatment	Number, Design	Quality	Applicability	Consistency	Diagnostic Accuracy or Magnitude of Effect (Including Precision)
Gonadal steroids	5 RCTs	Fair; short duration of followup	Older adults with mild to moderate dementia (AD only); populations from U.S., Europe, and Asia; doses of medications applicable to common use	Consistent finding of no benefit despite type of hormone	No benefit in global cognitive or physical function for estrogen ± progesterone (k=4; n=277); no benefit in global cognitive function for testosterone (k=1; n=18). Other outcomes sparsely reported.
Dietary supplements	12 RCTs	Fair to good	Broad range of older adults with mild to moderate dementia or MCI, mainly in people with AD; populations from U.S., northern Europe, and Asia	Consistent finding of no benefit despite type of dietary supplement	No benefit in global cognitive or physical function for dietary supplements, including multivitamins (k=1; n=89), B vitamins (k=7; n=1294), vitamins E ± C (k=3; n=522), or omega-3 fatty acids (k=4; n=1145). Other outcomes sparsely reported.
Nonpharmacologic interventions	93 RCTs	Fair to good (mostly fair)	Broad range of older adults with mild to moderate dementia or MCI; underrepresentation of nonwhite populations; many complex interventions may not be widely available in the U.S.	Inconsistencies by type of intervention. Inconsistencies within type of intervention may be due to differences in populations, details of intervention, and outcome measurement. Cannot evaluate inconsistency of other outcomes given sparse reporting.	For dementia, it appears that complex interventions aimed at caregivers or dyads of patients with moderate (as opposed to mild) dementia can result in small improvement in caregiver burden and depression, but the clinical significance of these small changes is not clear. For MCI or mild to moderate dementia, cognitive stimulation ± training can result in improvement in global cognitive function; however, the clinical significance of these changes is not clear given the sizeable imprecision around this benefit.
Caregiver (or dyad) interventions	59 RCTs	Fair to good	Broad range of older adults with mild to moderate dementia; populations from North America, Europe, Australia, and Asia; very wide range of types and intensity of interventions	Generally consistent for caregiver burden and depression outcomes; however, large clinical and statistical heterogeneity in types and components, intensity, and duration of interventions limits interpretation of point estimate(s) from pooled analyses. Cannot evaluate inconsistency of other outcomes given sparse reporting.	Most trials (k=52; n=8932) evaluated caregiver interventions with a psychoeducational component. Small to very small benefit in caregiver burden and depression for broad range of caregiver interventions with a psychoeducational component in the short-term (generally 3-12 months). Pooled analyses for both caregiver burden (k=24; n=2679) and depression (k=30; n=3537) outcomes showed a small benefit (SMD, -0.23 [95% CI, -0.35 to -0.12]; I^2=52.7; and for SMD, -0.21 [95% CI, -0.30 to -0.13]; I^2=34.1, respectively).

Table 16. Summary of Evidence

KQ, by Instrument or Treatment	Number, Design	Quality	Applicability	Consistency	Diagnostic Accuracy or Magnitude of Effect (Including Precision)
Cognitive training, rehabilitation, or stimulation ± motor training	15 RCTs	Fair	Broad range of older adults with mild to moderate dementia and MCI; populations in North American, Europe, and Australia	Unclear if inconsistency in findings for cognitive function were due to differences in study quality, populations, intervention type or intensity, or outcomes measured. Cannot evaluate inconsistency of other outcomes given sparse reporting.	Cognitive interventions (k=15; n=1128) had inconsistent findings of benefit. Cognitive stimulation ± cognitive training can improve cognitive function in people with MCI or mild dementia. Pooled analyses for global cognitive outcomes (k=6; n=513) showed a moderate benefit at 6 to 12 months (SMD, -0.59 [95% CI, -0.93 to -0.25]; I^2=52.7%). Confidence intervals were quite wide; therefore, the effect on global cognitive function can range from very small to moderate.
Exercise interventions	10 RCTs	Fair to good (mostly fair)	Broad range of older adults with mild to moderate dementia and MCI; populations in North America, Australia, and Hong Kong	Inconsistent; unclear if due to differences in study quality, population, intervention, or outcomes measured. Cannot evaluate other outcomes given sparse reporting.	Exercise interventions (k=10; n=1033) had inconsistent findings of benefit. However, selected, well-conducted studies suggest a small benefit in cognitive function in people with MCI (k=2; n=220) and physical function and HRQL in people with dementia (k=1; n=153).
Multidisciplinary interventions	5 RCTs	Fair	Older adults with either mild to moderate dementia or MCI; only one trial in the U.S., which was conducted in an assisted living facility, remaining trials conducted in Europe	Consistent finding of no benefit.	Multidisciplinary care interventions involving assessment and care coordination (k=5; n=1766) showed no benefit in global cognitive function, physical function, institutionalization, or HRQL.
Education only	2 RCTs	Fair	Older adults with mild to moderate dementia living in residential care facility in Australia or GP practices in Germany	Consistent finding of no benefit.	Two trials (n=741) aimed at educating residential care staff and/or GPs caring for people with dementia found no benefit in HRQL, neuropsychiatric disturbances, hospitalization, or institutionalization.
KQ 5	1 SER (50 RCTs), 40 RCTs, 6 OLEs, and 13 observation-al studies	Fair to good (mostly fair)	Broad range of older adults with both dementia and MCI; majority of studies from trial populations; poor representation of nonwhite populations	Generally consistent findings for FDA-approved medications for AD; however, cannot evaluate for other interventions given sparse reporting of adverse effects.	Adverse effects are not commonly reported in intervention trials and not described in the observational literature, with the exception of harms of AChEIs. AChEIs commonly have side effects that lead to discontinuation of medication.

Table 16. Summary of Evidence

KQ, by Instrument or Treatment	Number, Design	Quality	Applicability	Consistency	Diagnostic Accuracy or Magnitude of Effect (Including Precision)
FDA-approved medications for AD	1 SER (50 RCTs), 16 RCTs, 6 OLEs, and 13 cross-sectional, case-control, or cohort studies	Fair to good	Broad range of older adults with mild to moderate dementia and MCI; populations from North America, Europe, Australia, and Asia	Generally consistent findings by class effect (AChEI vs. NMDA receptor antagonist), estimation of frequency of adverse events may be higher in observational studies due to population selection (more restrictive for trials).	Discontinuation from AChEIs (k=45) but not memantine (k=9) is more common than placebo. Across trials, there does not appear to be a difference in total serious adverse events for any of these medications; however, tacrine trials did not report serious adverse events. Observational studies examining AChEIs (k=12; n=188,912) suggest that the most common serious adverse events are CNS, heart rate/rhythm, and GI disorders, and that bradycardia and adverse events related to bradycardia (e.g., fall, syncope) are increased due to their use.
Other medications	20 RCTs	Fair	Broad range of older adults with mild to moderate dementia and MCI; populations restricted to people enrolled in trials; populations from U.S., Europe, and Asia	Some minor inconsistencies by differences in type and dose of medication, population, and type of adverse effect reported.	Inconsistently reported in trials. No statistically significant differences in total adverse effects, serious adverse effects, or discontinuation of medication due to adverse effects, except for increased total adverse events and serious bleeding in persons taking ASA (k=1; n=310), increased withdrawal due to adverse events in people taking high-dose atorvastatin (k=1; n=640), increased syncope in residents of ALF receiving high-dose vitamin E (k=1; n=169), and increased vaginal bleeding in people taking estrogen replacement (k=1; n=50).
Nonpharmacologic interventions	4 RCTs	Fair	Broad range of older adults with mild to moderate dementia and MCI; populations restricted to trial populations	Few hypothesized harms; however, unclear consistency given adverse effects were rarely reported.	Harms were not reported for caregiver interventions, cognitive training or stimulation, or multidisciplinary care interventions. There was no evidence of increased total or serious adverse effects due to exercise interventions (k=4; n=439).

Abbreviations: AChEI = acetylcholinesterase inhibitor; AD8 = Ascertain Dementia 8; ADL = activities of daily living; AMT = Abbreviated Mental Test; CAMCI = Computer Assessment of Mild Cognitive Impairment; CDT = clock drawing test; CI = confidence interval; DX = diagnostic; FCRST = Free and Cued Selective Reminding Test; GPCOG = General Practitioner Assessment of Cognition; IADL = instrumental activities of daily living; IQCODE = informant Questionnaire on Cognitive Decline in the Elderly; KQ = key question; MCI = mild cognitive impairment; MIS(T) = Memory Impairment Screen by Telephone; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MSQ = Mental Status Questionnaire; NA = not applicable; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized, controlled trial; SER = systematic evidence review; Sn = sensitivity; Sp = specificity; SLUMS = St. Louis University Mental Status; SPMSQ = Short Portable Mental Status Questionnaire; TICS = Telephone Interview for Cognitive Status; TICS(M) = Telephone Interview for Cognitive Status Modified; VAT = Visual Association Test; 7MS = 7-Minute Screen.

Table 17. Positive and Negative Predictive Values for Various Sensitivity, Specificity, and Prevalence Percentages

Age (y)	Prevalence of Dementia	PPV 70/80*	PPV 70/90*	PPV 80/80*	PPV 90/80*	PPV 90/70*	NPV 70/80*	NPV 70/90*	NPV 80/80*	NPV 90/80*	NPV 90/70*
65-69	1	3.41	6.60	3.88	4.35	2.94	99.6	99.7	99.7	99.9	99.9
70-79	5	15.6	26.9	17.4	19.1	13.6	98.1	98.3	98.7	99.3	99.3
	10	28.0	43.8	30.8	33.3	25.0	96.0	96.4	97.3	98.6	98.4
80-84	15	38.2	55.3	41.3	44.3	34.6	93.8	94.4	95.8	97.8	97.5
	20	46.7	63.6	50.0	52.9	42.9	91.4	92.3	94.1	97.0	96.6
85+	25	53.8	70.0	57.1	60.0	50.0	88.9	90.0	92.3	96.0	95.5
	30	60.0	75.0	63.2	65.9	56.3	86.2	87.5	90.3	94.9	94.2
	40	70.0	82.4	72.7	75.0	66.7	80.0	81.8	85.7	92.3	91.3

* Sensitivity/Specificity.
Note: All prevalence, PPV, NPV, sensitivity, and specificity values are percentages.

Abbreviations: PPV = positive predictive value; NPV = negative predictive value.

Systematic Review Search Strategy

PubMed (3/18/2011)

1) "Dementia/diagnosis"[Majr:NoExp] OR "Dementia/diet therapy"[Majr:NoExp] OR "Dementia/drug therapy"[Majr:NoExp] OR "Dementia/epidemiology"[Majr:NoExp] OR "Dementia/prevention and control"[Majr:NoExp] OR "Dementia/psychology"[Majr:NoExp] OR "Dementia/therapy"[Majr:NoExp] OR "Alzheimer Disease/diet therapy"[Majr] OR "Alzheimer Disease/drug therapy"[Majr] OR "Alzheimer Disease/epidemiology"[Majr] OR "Alzheimer Disease/prevention and control"[Majr] OR "Alzheimer Disease/psychology"[Majr] OR "Alzheimer Disease/therapy"[Majr] OR "Delirium, Dementia, Amnestic, Cognitive Disorders/diagnosis"[Majr:NoExp] OR "Delirium, Dementia, Amnestic, Cognitive Disorders/diet therapy"[Majr:NoExp] OR "Delirium, Dementia, Amnestic, Cognitive Disorders/drug therapy"[Majr:NoExp] OR "Delirium, Dementia, Amnestic, Cognitive Disorders/epidemiology"[Majr:NoExp] OR "Delirium, Dementia, Amnestic, Cognitive Disorders/prevention and control"[Majr:NoExp] OR "Delirium, Dementia, Amnestic, Cognitive Disorders/psychology"[Majr:NoExp] OR "Delirium, Dementia, Amnestic, Cognitive Disorders/rehabilitation"[Majr:NoExp] OR "Delirium, Dementia, Amnestic, Cognitive Disorders/therapy"[Majr:NoExp] OR "Cognition Disorders/diagnosis"[Majr:NoExp] OR "Cognition Disorders/diet therapy"[Majr:NoExp] OR "Cognition Disorders/drug therapy"[Majr:NoExp] OR "Cognition Disorders/epidemiology"[Majr:NoExp] OR "Cognition Disorders/prevention and control"[Majr:NoExp] OR "Cognition Disorders/psychology"[Majr:NoExp] OR "Cognition Disorders/rehabilitation"[Majr:NoExp] OR "Cognition Disorders/therapy"[Majr:NoExp]
2) systematic[sb]
3) 1 AND 2
4) "Cochrane Database Syst Rev"[Journal] OR"Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal]
5) "Consensus Development Conference" [Publication Type] OR "Meta-Analysis" [Publication Type]
6) systematic*[tiab] OR meta analy*[tiab] OR literature[tiab] OR published[tiab] OR publication*[tiab] OR medline[tiab]
7) "Mass Screening"[Mesh:NoExp] OR screen*[ti]
8) 4 OR 5 OR 6 OR 7
9) 3 AND 8
10) (dementia[ti] OR alzheimer*[ti])
11) 10 AND 2
12) (in process[sb] OR publisher[sb] OR pubmednotmedline[sb])
13) 11 AND 12
14) mild cognitive impairment [ti] OR cognitive decline [ti]
15) 14 AND 2
16) 9 OR 13 OR 15
17) 9 OR 13 OR 15 Limits: English, Publication Date from 2001 to 2012

Screening Literature Search Strategies, 12/8/2012

Dementia screening trials

Date limit: 2000-present (bridging from previous Task Force review)

Database(s): Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2012, Ovid MEDLINE(R) 1988 to 1995, Ovid MEDLINE(R) Daily Update December 8, 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 8, 2012

#	Searches
1	Dementia/
2	Alzheimer Disease/
3	Aphasia, Primary Progressive/
4	Dementia, Vascular/
5	Dementia, Multi-Infarct/
6	Frontotemporal Dementia/
7	Delirium, Dementia, Amnestic, Cognitive Disorders/
8	dementia.ti.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	screen$.ti,ab.
11	mass screening/
12	10 or 11
13	9 and 12
14	*Dementia/di [Diagnosis]
15	*Alzheimer Disease/di [Diagnosis]
16	*Delirium, Dementia, Amnestic, Cognitive Disorders/di [Diagnosis]
17	13 or 14 or 15 or 16
18	(clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
19	random$.ti,ab.
20	Clinical Trials as Topic/
21	Randomized Controlled Trials as Topic/
22	clinical trial$.ti,ab.
23	controlled trial$.ti,ab.
24	18 or 19 or 20 or 21 or 22 or 23
25	17 and 24
26	limit 25 to english language
27	limit 26 to yr="2000 -Current"

Mild cognitive impairment screening trials

Date limit: 1990-present

Database(s): Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2012, Ovid MEDLINE(R) 1988 to 1995, Ovid MEDLINE(R) Daily Update December 8, 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 8, 2012

#	Searches
1	Cognition Disorders/
2	cognitive impairment$.ti.
3	cognitive decline.ti.
4	cognitive loss.ti.
5	cognitive disorder$.ti.
6	1 or 2 or 3 or 4 or 5
7	screen$.ti,ab.
8	mass screening/
9	7 or 8
10	6 and 9
11	*Cognition Disorders/di [Diagnosis]
12	10 or 11
13	(clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
14	random$.ti,ab.
15	Clinical Trials as Topic/
16	Randomized Controlled Trials as Topic/
17	clinical trial$.ti,ab.
18	controlled trial$.ti,ab.
19	13 or 14 or 15 or 16 or 17 or 18
20	12 and 19
21	limit 20 to english language
22	limit 21 to yr="1990 -Current"

Test performance of screening instruments for dementia
Date limit: 2006-present (bridging from Holsinger review)

Database(s): Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2012, Ovid MEDLINE(R) 1988 to 1995, Ovid MEDLINE(R) Daily Update December 8, 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 8, 2012

#	Searches
1	Dementia/
2	Alzheimer Disease/
3	Aphasia, Primary Progressive/
4	Dementia, Vascular/
5	Dementia, Multi-Infarct/
6	Frontotemporal Dementia/
7	Delirium, Dementia, Amnestic, Cognitive Disorders/
8	dementia.ti.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	"Sensitivity and Specificity"/
11	"Predictive Value of Tests"/
12	ROC Curve/
13	sensitivit$.ti,ab.

14 predictive value.ti,ab.
15 accuracy.ti,ab.
16 False Negative Reactions/
17 False Positive Reactions/
18 Diagnostic Errors/
19 "Reproducibility of Results"/
20 Reference Values/
21 Reference Standards/
22 Observer Variation/
23 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 9 and 23
25 limit 24 to english language
26 limit 25 to yr="2006 -Current"

Test performance of screening instruments for mild cognitive impairment
Date limit: 1990-present

Database(s): Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2012, Ovid MEDLINE(R) 1988 to 1995, Ovid MEDLINE(R) Daily Update December 8, 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 8, 2012

#	Searches
1	*Cognition Disorders/di [Diagnosis]
2	cognitive impairment$.ti.
3	cognitive decline.ti.
4	cognitive loss.ti.
5	cognitive disorder$.ti.
6	1 or 2 or 3 or 4 or 5
7	"Sensitivity and Specificity"/
8	"Predictive Value of Tests"/
9	ROC Curve/
10	sensitivit$.ti,ab.
11	predictive value.ti,ab.
12	accuracy.ti,ab.
13	False Negative Reactions/
14	False Positive Reactions/
15	Diagnostic Errors/
16	"Reproducibility of Results"/
17	Reference Values/
18	Reference Standards/
19	Observer Variation/
20	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	6 and 20
22	limit 21 to english language
23	limit 22 to yr="1990 -Current"

Dementia
Screening harms
Date limit: 2000-present (bridging from previous Task Force review)

Database(s): Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2012, Ovid MEDLINE(R) 1988 to 1995, Ovid MEDLINE(R) Daily Update December 8, 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 8, 2012

#	Searches
1	Dementia/
2	Alzheimer Disease/
3	Aphasia, Primary Progressive/
4	Dementia, Vascular/
5	Dementia, Multi-Infarct/
6	Frontotemporal Dementia/
7	Delirium, Dementia, Amnestic, Cognitive Disorders/
8	dementia.ti.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	screen$.ti,ab.
11	mass screening/
12	10 or 11
13	9 and 12
14	*Dementia/di [Diagnosis]
15	*Alzheimer Disease/di [Diagnosis]
16	*Delirium, Dementia, Amnestic, Cognitive Disorders/di [Diagnosis]
17	13 or 14 or 15 or 16
18	adverse effects.fs.
19	adverse$.ti,ab.
20	harm$.ti,ab.
21	Anxiety/
22	anxiety.ti,ab.
23	Depression/
24	depression.ti,ab.
25	Depressive Disorder/
26	labeling.ti,ab.
27	labelling.ti,ab.
28	labeled.ti,ab.
29	labelled.ti,ab.
30	Stress, Psychological/
31	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	17 and 31
33	limit 32 to english language
34	limit 33 to yr="2000 -Current"

Mild cognitive impairment
Screening harms
Date limit: 1990-present

Database(s): Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2012, Ovid MEDLINE(R) 1988 to 1995, Ovid MEDLINE(R) Daily Update December 8, 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 8, 2012

#	Searches
1	Cognition Disorders/
2	cognitive impairment$.ti.
3	cognitive decline.ti.
4	cognitive loss.ti.
5	cognitive disorder$.ti.
6	1 or 2 or 3 or 4 or 5
7	screen$.ti,ab.
8	mass screening/
9	7 or 8
10	6 and 9
11	*Cognition Disorders/di [Diagnosis]
12	10 or 11
13	adverse effects.fs.
14	adverse$.ti,ab.
15	harm$.ti,ab.
16	Anxiety/
17	anxiety.ti,ab.
18	Depression/
19	depression.ti,ab.
20	Depressive Disorder/
21	labeling.ti,ab.
22	labelling.ti,ab.
23	labeled.ti,ab.
24	labelled.ti,ab.
25	Stress, Psychological/
26	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27	12 and 26
28	limit 27 to english language
29	limit 28 to yr="1990 -Current"

All screening questions
Cochrane Central Register of Controlled Trials (Central)
Issue 3 of 4, Jul 2011

#1 Dementia:ti,kw OR Alzheimer*:kw, from 2000 to 2012 in Clinical Trials
#2 screen*:ti,ab,kw, from 2000 to 2012 in Clinical Trials
#3 (#1 AND #2), from 2000 to 2012
#4 (cognitive next impairment*):ti,kw, from 1990 to 2012 in Clinical Trials
#5 (cognitive next decline):ti,kw, from 1990 to 2012 in Clinical Trials
#6 (cognitive next loss):ti,kw, from 1990 to 2012 in Clinical Trials
#7 (cognitive next disorder*):ti,kw, from 1990 to 2012 in Clinical Trials
#8 (Cognition next Disorders):kw, from 1990 to 2012 in Clinical Trials
#9 (#4 OR #5 OR #6 OR #7 OR #8), from 1990 to 2012
#10 screen*:ti,ab,kw, from 1990 to 2012 in Clinical Trials
#11 (#9 AND #10), from 1990 to 2012
#12 sensitivit*:ti,ab,kw, from 2006 to 2012 in Clinical Trials
#13 (ROC next Curve):ti,ab,kw, from 2006 to 2012 in Clinical Trials
#14 (predictive next value):ti,ab,kw, from 2006 to 2012 in Clinical Trials
#15 accuracy:ti,ab,kw, from 2006 to 2012 in Clinical Trials
#16 (False next Negative*):ti,ab,kw, from 2006 to 2012 in Clinical Trials
#17 (False next positive*):ti,ab,kw, from 2006 to 2012 in Clinical Trials
#18 (Diagnostic next Error*):ti,ab,kw, from 2006 to 2012 in Clinical Trials
#19 Reproducibility:ti,ab,kw, from 2006 to 2012 in Clinical Trials
#20 (Reference next Value*):ti,ab,kw, from 2006 to 2012 in Clinical Trials
#21 (Reference next standard*):ti,ab,kw, from 2006 to 2012 in Clinical Trials
#22 (Observer next Variation*):ti,ab,kw, from 2006 to 2012 in Clinical Trials
#23 (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22), from 2006 to 2012
#24 (#1 AND #23), from 2006 to 2012
#25 sensitivit*:ti,ab,kw,, from 1990 to 2012 in Clinical Trials
#26 (ROC next Curve):ti,ab,kw, from 1990 to 2012 in Clinical Trials
#27 (predictive next value):ti,ab,kw, from 1990 to 2012 in Clinical Trials
#28 accuracy:ti,ab,kw, from 1990 to 2012 in Clinical Trials
#29 (False next Negative*):ti,ab,kw, from 1990 to 2012 in Clinical Trials
#30 (False next positive*):ti,ab,kw, from 1990 to 2012 in Clinical Trials
#31 (Diagnostic next Error*):ti,ab,kw, from 1990 to 2012 in Clinical Trials
#32 Reproducibility:ti,ab,kw, from 1990 to 2012 in Clinical Trials
#33 (Reference next Value*):ti,ab,kw, from 1990 to 2012 in Clinical Trials
#34 (Reference next standard*):ti,ab,kw, from 1990 to 2012 in Clinical Trials
#35 (Observer next Variation*):ti,ab,kw, from 1990 to 2012 in Clinical Trials
#36 (#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35), from 1990 to 2012
#37 (#9 AND #36), from 1990 to 2012
#38 (#3 OR #11 OR #24 OR #37)

PsycINFO 1987 to December Week 1 2012

#	**Searches**
1	Dementia/
2	Senile Dementia/
3	Vascular Dementia/

4 Alzheimer's Disease/
5 1 or 2 or 3 or 4
6 Screening/
7 Health Screening/
8 Screening Tests/
9 screen$.ti,ab.
10 6 or 7 or 8 or 9
11 5 and 10
12 treatment outcome clinical trial.md.
13 experiment controls/
14 controlled trial$.ti,ab,id,hw.
15 clinical trial$.ti,ab,id,hw.
16 random$.ti,ab,id,hw.
17 Anxiety/
18 Anxiety Disorders/
19 "Depression (Emotion)"/
20 Labeling/
21 Psychological Stress/
22 adverse$.ti,ab.
23 harm$.ti,ab.
24 anxiety.ti,ab.
25 depression.ti,ab.
26 labeling.ti,ab.
27 labelling.ti,ab.
28 labeled.ti,ab.
29 labelled.ti,ab.
30 or/12-29
31 11 and 30
32 limit 31 to english language
33 limit 32 to yr="2000 -Current"
34 Cognitive Impairment/
35 cognitive impairment$.ti.
36 cognitive decline.ti.
37 cognitive loss.ti.
38 cognitive disorder$.ti.
39 or/34-38
40 39 and 10 and 30
41 limit 40 to english language
42 limit 41 to yr="1990 -Current"
43 Test Reliability/
44 Test Validity/
45 sensitivit$.ti,ab.
46 predictive value.ti,ab.
47 accuracy.ti,ab.
48 or/43-47
49 5 and 48

50 limit 49 to english language
51 limit 50 to yr="2006 -Current"
52 39 and 48
53 limit 52 to english language
54 limit 53 to yr="1990 -Current"
55 33 or 42 or 51 or 54

Treatment Literature Search Strategies

Database(s): Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2012, Ovid MEDLINE(R) 1988 to 1995, Ovid MEDLINE(R) Daily Update December 8, 2012 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 8, 2012

#	Searches
1	Dementia/
2	Alzheimer Disease/
3	Aphasia, Primary Progressive/
4	Dementia, Vascular/
5	Dementia, Multi-Infarct/
6	Frontotemporal Dementia/
7	Delirium, Dementia, Amnestic, Cognitive Disorders/
8	dementia.ti.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	Cognition Disorders/
11	cognitive impairment$.ti.
12	cognitive decline.ti.
13	cognitive loss.ti.
14	cognitive disorder$.ti.
15	10 or 11 or 12 or 13 or 14
16	clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/
17	(clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
18	control groups/ or double-blind method/ or single-blind method/
19	random$.ti,ab.
20	placebo*.ti,ab.
21	clinical trial$.ti,ab.
22	controlled trial$.ti,ab.
23	16 or 17 or 18 or 19 or 20 or 21 or 22
24	9 and 23
25	15 and 23
26	statin$.mp.
27	Hydroxymethylglutaryl-CoA Reductase Inhibitors/
28	lovastatin.mp.
29	simvastatin.mp.
30	cerivastatin.mp.
31	atorvastatin.mp.

32 rosuvastatin.mp.
33 pravastatin.mp.
34 fluvastatin.mp.
35 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36 24 and 35
37 limit 36 to yr="2008 -Current"
38 25 and 35
39 limit 38 to yr="1990 -Current"
40 Antihypertensive Agents/
41 Antihypertensive*.ti,ab.
42 Diuretics/
43 Diuretic*.ti,ab.
44 exp Adrenergic beta-Antagonists/
45 Adrenergic beta Antagonist*.ti,ab.
46 beta blocker*.ti,ab.
47 exp Adrenergic alpha-Antagonists/
48 Adrenergic alpha Antagonist*.ti,ab.
49 alpha blocker*.ti,ab.
50 Angiotensin-Converting Enzyme Inhibitors/
51 ace inhibitor*.ti,ab.
52 Angiotensin Converting Enzyme Inhibitor*.ti,ab.
53 Calcium Channel Blockers/
54 Calcium Channel Blocker*.ti,ab.
55 Vasodilator Agents/
56 Vasodilator*.ti,ab.
57 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or
58 24 and 57
59 limit 58 to yr="2000 -Current"
60 25 and 57
61 limit 60 to yr="1990 -Current"
62 Aspirin/
63 aspirin*.ti,ab.
64 62 or 63
65 24 and 64
66 limit 65 to yr="2007 -Current"
67 25 and 64
68 limit 67 to yr="1990 -Current"
69 Anti-Inflammatory Agents, Non-Steroidal/
70 Nonsteroidal Anti Inflammatory Agent*.ti,ab.
71 Non steroidal Anti Inflammatory Agent*.ti,ab.
72 Nonsteroidal Antiinflammatory Agent*.ti,ab.
73 Non steroidal Antiinflammatory Agent*.ti,ab.
74 NSAID*.ti,ab.
75 Diclofenac/
76 Diclofenac.ti,ab.
77 Ibuprofen/

78 Ibuprofen.ti,ab.
79 Indomethacin/
80 Indomethacin.ti,ab.
81 Ketoprofen/
82 Ketoprofen.ti,ab.
83 Ketorolac/
84 Ketorolac.ti,ab.
85 Naproxen/
86 Naproxen.ti,ab.
87 Piroxicam/
88 Piroxicam.ti,ab.
89 Salicylates/
90 Salicylate*.ti,ab.
91 Sulindac/
92 Sulindac.ti,ab.
93 Cyclooxygenase Inhibitors/
94 Cyclooxygenase Inhibitor*.ti,ab.
95 Cyclooxygenase 2 Inhibitors/
96 Cyclooxygenase 2 Inhibitor*.ti,ab.
97 COX 2 Inhibitor*.ti,ab.
98 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97
99 24 and 98
100 limit 99 to yr="2000 -Current"
101 25 and 98
102 limit 101 to yr="1990 -Current"
103 Gonadal Steroid Hormones/
104 Hormone Replacement Therapy/
105 Estrogen Replacement Therapy/
106 Estradiol/
107 Estrogens/
108 "Estrogens, Conjugated (USP)"/
109 Medroxyprogesterone Acetate/
110 Progesterone/
111 Progesterone Congeners/
112 Androgens/
113 Testosterone/
114 Dehydroepiandrosterone/
115 Dehydroepiandrosterone Sulfate/
116 Norethindrone/
117 Hormone Replacement Therapy.ti,ab.
118 estrogen*.ti,ab.
119 Estradiol.ti,ab.
120 Medroxyprogesterone.ti,ab.
121 Progesterone.ti,ab.
122 Androgens.ti,ab.

123 Testosterone.ti,ab.
124 Dehydroepiandrosterone.ti,ab.
125 Norethindrone.ti,ab.
126 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125
127 24 and 126
128 limit 127 to yr="2000 -Current"
129 25 and 126
130 limit 129 to yr="1990 -Current"
131 Cholinesterase inhibitors/
132 Cholinesterase Inhibitor*.ti,ab.
133 Anticholinesterase*.ti,ab.
134 Galantamine/
135 Galantamine.ti,ab.
136 Tacrine/
137 Tacrine.ti,ab.
138 rivastigmine.ti,ab.
139 donepezil.ti,ab.
140 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139
141 24 and 140
142 limit 141 to yr="2006 -Current"
143 25 and 140
144 limit 143 to yr="2006 -Current"
145 Memantine/
146 Memantine.ti,ab.
147 145 or 146
148 24 and 147
149 limit 148 to yr="2006 -Current"
150 25 and 147
151 limit 150 to yr="2006 -Current"
152 folic acid/
153 folic acid.ti,ab.
154 folate.ti,ab.
155 Vitamin B Complex/
156 Thiamine/
157 Thiamine.ti,ab.
158 Thiamin.ti,ab.
159 Thiamine Monophosphate/
160 Thiamine Pyrophosphate/
161 Thiamine Triphosphate/
162 Vitamin B 1.ti,ab.
163 Vitamin B1.ti,ab.
164 Riboflavin/
165 Riboflavin.ti,ab.
166 Vitamin B 2.ti,ab.
167 Vitamin B2.ti,ab.

168 Vitamin B 6/
169 Vitamin B 6.ti,ab.
170 Vitamin B6.ti,ab.
171 Pyridoxine/
172 Pyridoxine.ti,ab.
173 Vitamin B 12/
174 Vitamin B 12.ti,ab.
175 Vitamin B12.ti,ab.
176 Cobamides/
177 Hydroxocobalamin/
178 Cobalamin.ti,ab.
179 Cyanocobalamin.ti,ab.
180 Cobamides.ti,ab.
181 Hydroxocobalamin.ti,ab.
182 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181
183 24 and 182
184 limit 183 to yr="2004 -Current"
185 25 and 182
186 limit 185 to yr="2004 -Current"
187 Antioxidants/
188 Antioxidant*.ti,ab.
189 Vitamin E/
190 Vitamin E.ti,ab.
191 alpha-Tocopherol/
192 Tocopherols/
193 Tocopherol*.ti,ab.
194 Ascorbic acid/
195 Ascorbic acid.ti,ab.
196 Vitamin C.ti,ab.
197 ascorbate.ti,ab.
198 beta carotene/
199 beta carotene.ti,ab.
200 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199
201 24 and 200
202 limit 201 to yr="2005 -Current"
203 25 and 200
204 limit 203 to yr="2005 -Current"
205 fatty acids, omega-3/ or alpha-linolenic acid/ or docosahexaenoic acids/ or neuroprostanes/ or eicosapentaenoic acid/
206 Omega 3.ti,ab.
207 n 3 Fatty Acid*.ti,ab.
208 Linolenic Acids/
209 Linolenic Acid*.ti,ab.
210 Fatty Acids, Essential/

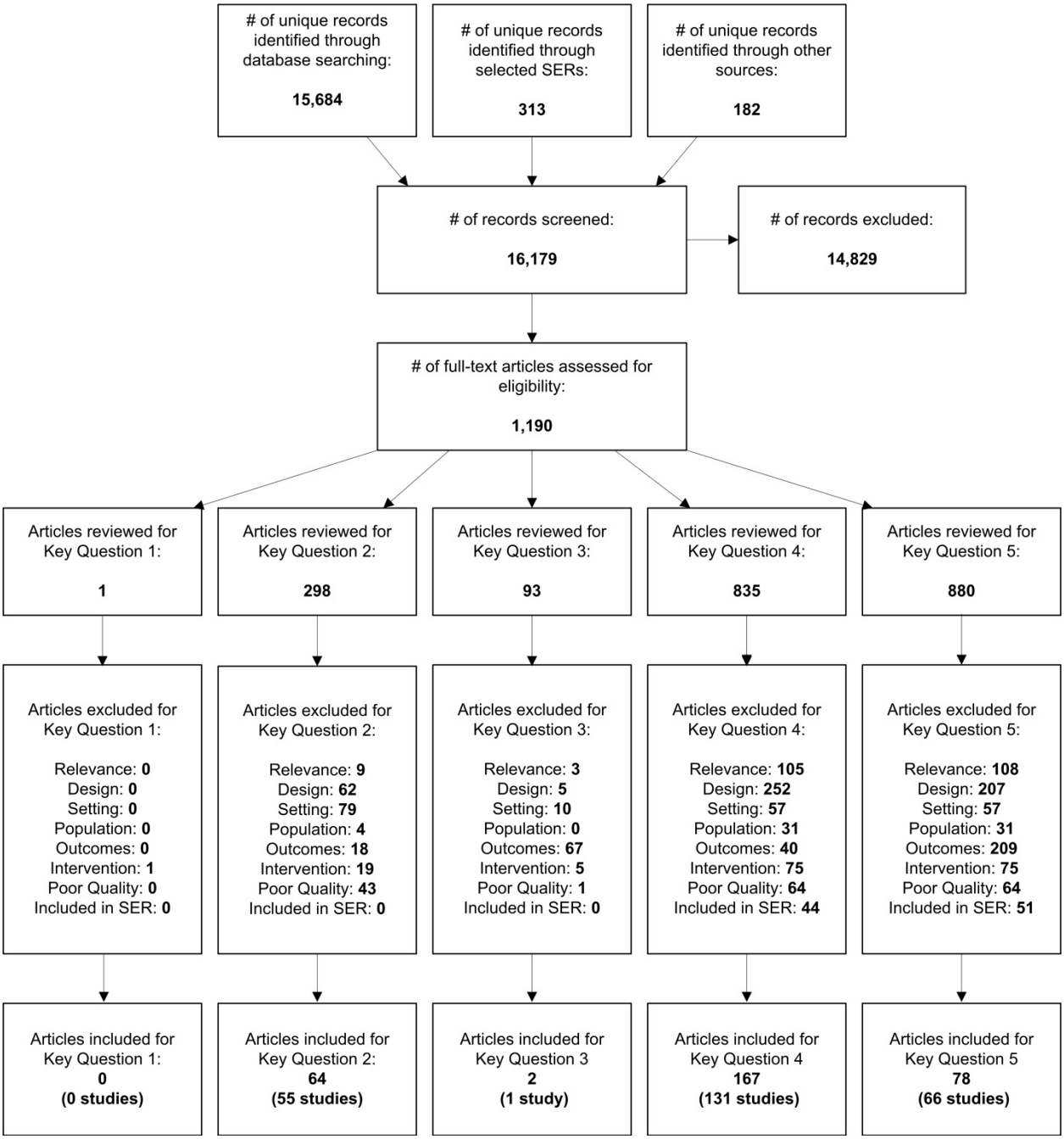
211 Dietary Fats, Unsaturated/
212 Fish Oils/
213 fish oil*.ti,ab.
214 diet* fatty acid*.ti,ab.
215 Diet, Mediterranean/
216 Mediterranean diet*.ti,ab.
217 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216
218 24 and 217
219 limit 218 to yr="2005 -Current"
220 25 and 217
221 limit 220 to yr="2005 -Current"
222 Exercise/
223 Exercise Therapy/
224 Physical Fitness/
225 Walking/
226 exercis*.ti,ab.
227 physical activity.ti,ab.
228 physical training.ti,ab.
229 strength training.ti,ab.
230 resistance training.ti,ab.
231 Resistance Training/
232 aerobic training.ti,ab.
233 cardiovascular training.ti,ab.
234 endurance training.ti,ab.
235 flexibility training.ti,ab.
236 Relaxation/
237 relaxation.ti,ab.
238 Tai Ji/
239 Tai Chi.ti,ab.
240 walking.ti,ab.
241 Yoga/
242 yoga.ti,ab.
243 Dancing/
244 (dancing or dance).ti,ab.
245 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244
246 24 and 245
247 limit 246 to yr="2007 -Current"
248 25 and 245
249 limit 248 to yr="1990 -Current"
250 Caregivers/
251 caregiver*.ti,ab.
252 caregiving.ti,ab.
253 (carer or carers).ti,ab.
254 Self-Help Groups/
255 self help.ti,ab.

256 Respite Care/
257 care giver*.ti,ab.
258 Respite Care/
259 respite.ti,ab.
260 Family Therapy/
261 family therapy.ti,ab.
262 Social Support/
263 social support*.ti,ab.
264 Day Care/
265 (day care or daycare).ti,ab.
266 skills training.ti,ab.
267 Health Education/
268 health education.ti,ab.
269 education.fs.
270 education, continuing/ or education, medical, continuing/ or education, nursing, continuing/
271 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270
272 24 and 271
273 limit 272 to yr="2000 -Current"
274 Counseling/
275 Directive Counseling/
276 Cognitive Therapy/
277 cognitive therapy.ti,ab.
278 psychotherapy/ or psychotherapy, brief/
279 Behavior Therapy/
280 psychotherap*.ti,ab.
281 counsel*.ti,ab.
282 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281
283 24 and 282
284 limit 283 to yr="2000 -Current"
285 25 and 282
286 limit 285 to yr="1990 -Current"
287 (cognitive* adj3 engage*).ti,ab.
288 (creative* adj3 engage*).ti,ab.
289 (cognitive* adj3 stimulat*).ti,ab.
290 cognitive training.ti,ab.
291 cognitive intervention*.ti,ab.
292 group reminiscence.ti,ab.
293 reality orientation.ti,ab.
294 Reality Therapy/
295 reality therapy.ti,ab.
296 cognitive exercis*.ti,ab.
297 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296
298 24 and 297
299 limit 298 to yr="2000 -Current"
300 25 and 297

301 limit 300 to yr="1990 -Current"
302 Case Management/
303 Patient Care Management/
304 care manage*.ti,ab.
305 case manage*.ti,ab.
306 302 or 303 or 304 or 305
307 24 and 306
308 limit 307 to yr="2000 -Current"
309 25 and 306
310 limit 309 to yr="1990 -Current"
311 ((multicomponent or multi component or multidisciplinary or multi disciplinary or multimodal or multi modal) adj3 (treatment* or program* or intervention*)).ti,ab.
312 24 and 311
313 limit 312 to yr="2000 -Current"
314 25 and 311
315 limit 314 to yr="1990 -Current"
316 37 or 39 or 59 or 61 or 66 or 68 or 100 or 102 or 128 or 130 or 142 or 144 or 149 or 151 or 184 or 186 or 202 or 204 or 219 or 221 or 247 or 249 or 273 or 284 or 286 or 299 or 301 or 308 or 310 or 313 or 315
317 limit 316 to english language
318 limit 317 to humans
319 limit 317 to animals
320 319 not 318
321 317 not 320
322 remove duplicates from 321

Appendix A. Detailed Methods

Figure 1. Literature Flow Diagram



Abbreviations: SER = systematic evidence review.

Appendix A. Detailed Methods

Table 1. Systematic Reviews Used for Their References and Search Dates of Literature Searches

Screening method/treatment intervention	Condition of interest	Primary existing systematic review used*	Other systematic review(s) to locate primary research
KQs 1–3			
Screening	MCI	None	Lonie, 2009[1] Ehreke, 2010[2] Mitchell, 2009[3]
	Dementia	Holsinger[4]	Mitchell, 2010[5] Mitchell, 2010[6] Kansagara, 2010[7] Mitchell, 2009[3] Castilla-Rilo, 2007[8] Cherbuin, 2008[9] Milne, 2008[10]
Screening harms	MCI/Dementia	None	Kansagara, 2010[7]
KQs 4–5: Pharmacologic			
Statins	MCI	None	None
	Dementia	McGuinness, 2010[11]	Plassman[12]
Harms of statins	MCI/Dementia	None	None
Antihypertensives	MCI	None	None
	Dementia	None	Plassman, 2010[12] Shah, 2009[13] Langa, 2004 [14]
Harms of antihypertensives	MCI/Dementia	None	None
NSAIDs (includes ASA)	MCI	None	None
	Dementia	Rands, 2000[15]	Plassman[12] Tabet (ibuprofen)[16] Tabet (indomethacin)[17]
Harms of NSAIDs	MCI/Dementia	None	None
Steroids (estrogen, testosterone)	MCI	None	None
	Dementia	None	Plassman[12] Hogervorst, 2009[18]
Harms of steroids	MCI/Dementia	None	None
Cholinesterase Inhibitors	MCI	Raina, 2008[19]	None
	Dementia	Raina, 2008[19]	Plassman[12] NICE 2011
Harms of cholinesterase inhibitors)	MCI/Dementia	None	None
Memantine	MCI	Raina, 2008[19]	None
	Dementia	Raina, 2008[19]	Plassman[12]
Harms of memantine	MCI/Dementia	None	
Vitamin B/folate	MCI	Malouf 2003[20] Malouf 2003[21] Malouf 2008[22] Balk 2006[23]	Jia 2008[24]
	Dementia	Malouf 2003[20] Malouf 2003[21] Malouf 2008[22] Jia 2008[24] Balk 2006[23]	Plassman 2010[12] Wald 2010[25] Dangour 2010[26]
Harms of vitamin B/folate	MCI/Dementia	Balk 2006[23]	None
Antioxidants (vitamin C, vitamin E, beta-carotene)	MCI	Jia 2008[24]	Issac 2008 (vitamin E)[27]
	Dementia	Jia 2008[24]	Plassman 2010[12] Boothby 2005[28] Issac 2008 (vitamin E)[27]
Harms of antioxidant vitamins	MCI/Dementia	None	None
Omega-3	MCI	Jia 2008[24] Issa 2006[29]	None
	Dementia	Jia, 2008[24] Issa 2006[29]	Plassman 2010[12] Dangour 2010[26] MacLean 2005[30]
Harms of omega-3	MCI/Dementia	None	None

Appendix A. Detailed Methods

Screening method/treatment intervention	Condition of interest	Primary existing systematic review used*	Other systematic review(s) to locate primary research
KQs 4–5: Nonpharmacologic			
Physical Activity	MCI	van Uffelen 2008[31]	None
	Dementia	van Uffelen 2008[31] Forbes 2008[32]	Plassman 2010[12] Olazaran 2010[33]
Harms of physical activity	MCI/Dementia	None	None
Counseling	MCI	None	None
	Dementia	None	Plassman 2010[12] Bates 2004[34] Olazaran 2010[33]
Harms of counseling	MCI/Dementia	None	None
Caregiver	MCI	Not applicable	Not applicable
	Dementia	Brodaty 2003[35] Lee 2004[36]	Plassman 2010[12] Chien 2011[37] Cooper 2007[38] Schoenmakers 2010[39] Selwood 2007[40] Smits 2007[41] Thompson 2007[42] Spijker 2008 Olazaran 2010[33] Pinquart 2006[43]
Harms of caregiver interventions	MCI/Dementia	None	None
Cognitive engagement	MCI	None	Jean 2010[44]
	Dementia	None	Plassman 2010[12] Frank 2005[45] Olazaran 2010
Harms of cognitive engagement	MCI/Dementia	None	None
Multicomponent	MCI	None	None
	Dementia	None	Pimouguet[46] Plassman[12] Bates 2004[34] Olazaran 2010[33]
Harms of multicomponent interventions	MCI/Dementia	None	None

* The start date for searches is 1 year prior to the end search date used in the primary existing systematic review. MCI literature was always searched from 1990 to present.

Abbreviations: ASA = acetylsalicyclic acid; KQ = key question; MCI = Mild Cognitive Impairment; NSAID = nonsteroidal anti-inflammatory drug.

Appendix A. Detailed Methods

Table 2. Inclusion/Exclusion Criteria

Populations	***Include***	Patient: Community-dwelling older adults, average age 65 years or older, generally asymptomatic but can have common symptoms like subjective memory complaints (SMC) Informal caregiver: Engaged in taking some kind of responsibility for the care of the patient; relationship such as spouse, de-facto partner, relative, or friend; can receive caregiver's pension
	Exclude	Patient: Populations exclusively with HIV/AIDS, Down syndrome, posttraumatic brain injuries, Parkinson's disease, and stroke Professional caregiver: Formally or professionally trained, paid salary
Settings	***Include***	Primary care, outpatient settings (ambulatory care), home, residential care facilities, assisted living, adult foster care in developed countries ("Very High" on the Human Development Index: Norway, Australia, New Zealand, United States, Ireland, Liechtenstein, Netherlands, Canada, Sweden, Germany, Japan, Republic of Korea, Switzerland, France, Israel, Finland, Iceland, Belgium, Denmark, Spain, Hong Kong, Greece, Italy, Luxembourg, Austria, United Kingdom, Singapore, Czech Republic, Slovenia, Andorra, Slovakia, United Arab Emirates, Malta, Estonia, Cyprus, Hungary, Brunei Darussalam, Qatar, Bahrain, Portugal, Poland, Barbados)
	Exclude	Hospital, long-term care facilities (e.g., skilled nursing facilities), emergency departments Screening: Participants recruited from memory, dementia, geropsychology, and neurology clinics
Disease/ Condition	***Include***	Screening: Any cognitive impairment (MCI or dementia) Treatment: MCI or early (mild-moderate) dementia (Functional Assessment Screening Test [FAST] stages 2-6)
	Exclude	Screening: None Treatment: Late (severe) dementia (severe dementia defined as FAST stage 7: very severe cognitive decline that includes loss of ADLs, IADLs, and verbal abilities), reversible causes of cognitive impairment
Screening	***Include***	Any screening instrument that can be delivered in primary care in ≤10 min for clinician administration or ≤20 min self-administration; informant instruments
	Exclude	Instruments that take >10 min for clinician administration or >20 min for self-administration; biomarkers (CSF, plasma, urine) or imaging (CT, MRI, PET); proxy respondents
Treatment/ management interventions	***Include***	Pharmacologic interventions used to treat patients with early (mild-moderate) dementia or MCI for the purpose of preventing cognitive decline; when applicable, treatments reviewed will be specific to specific types of dementia Nonpharmacologic interventions aimed at patients and/or caregivers given in early (mild-moderate) dementia or MCI; when applicable, treatments reviewed will be specific to specific types of dementia Treatments for this review will include: dietary supplements (B vitamins and folate, vitamins C, E, beta-carotene, and omega-3 fatty acids); medications (statins, antihypertensives, NSAIDs, gonadal steroids, cholinesterase inhibitors, memantine); social or behavioral interventions (physical activity, counseling, cognitive engagement, caregiver interventions, multidisciplinary or multicomponent interventions)
	Exclude	Treatments for symptom management (e.g., agitation, psychosis, depression) in dementia (i.e., antipsychotics, antiepileptics, antidepressants, SSRIs); medications not FDA-approved for treatment of dementia; herbal supplements (e.g., ginkgo biloba, DHEA); experimental or emerging therapies (antiamyloid disease modifying treatments)
Comparisons	***Include***	Diagnostic accuracy (KQ 2): Comparator needs to be reference standard Therapeutic or outcome efficacy (KQs 1,3–5): No screening/treatment or usual care
	Exclude	None
Outcomes – diagnostic accuracy	***Include***	Sensitivity, specificity, likelihood ratios, positive predictive value (PPV), negative predictive value (NPV)
	Exclude	Cost-related outcomes
Outcomes – decision-making, planning	***Include***	For patients, family/caregivers: Health care, legal, and financial planning (e.g., advanced directives); safety planning; living arrangements For clinicians: Health care planning, including advanced directives; patient and caregiver education; safety planning (change, monitored medication use); screening and diagnostic decisions (e.g., cancer screening); and other treatment or management decisions (e.g., treatment of reversible causes of dementia)
	Exclude	Cost-related outcomes

Outcomes – patient	***Include***	Safety (falls, other accidents), HRQL, cognitive function/decline, overall function/decline (ADL/IADL), unanticipated health care utilization (emergency use/hospitalizations), independent living (institutionalizations), medication adherence/compliance/errors, symptoms (insomnia, depression, agitation)
	Exclude	Cost-related outcomes; patient satisfaction (other than HRQL)
Outcomes – family/ caregiver	***Include***	HRQL, caregiver burden (a priori defined primary or secondary outcome in the trial, Zarit scale, Caregiver Activity Survey [CAS], Caregiver Strain Index, general measures of illness, depression/anxiety, and self-rated health)
	Exclude	Cost-related outcomes; family/caregiver satisfaction (other than caregiver burden and HRQL)
Outcomes – society	***Include***	Safety (automobile accidents)
	Exclude	Cost-related outcomes
Harms	***Include***	Screening: Diagnostic inaccuracy, paradoxical effects (unwanted or unexpected direction of effects of outcomes), psychological harms (depression, anxiety), harms due to labeling (psychological harms, insurance status) Treatment: Serious adverse events (e.g., death, serious adverse drug reactions), unexpected medical attention (e.g., emergency department visits, hospitalizations), paradoxical effects (unwanted or unexpected direction of effects of outcomes), psychological harms (depression, anxiety)
	Exclude	Screening: Patient or family/ caregiver dissatisfaction (other than psychological harms or patient adherence) Treatment: Patient or family/ caregiver dissatisfaction (other than psychological harms or patient adherence)
Study Designs	***Include***	Diagnostic accuracy (KQ 2): Good-quality systematic reviews, diagnostic accuracy studies Therapeutic or outcome efficacy (KQs 1, 4): good-quality systematic reviews, RCT/CCT Harms (KQs 3,5): good-quality systematic reviews, RCT/CCT, prospective observational studies for efficacy, retrospective and case-control studies for harms
	Exclude	All KQs: Poor-quality studies Therapeutic or outcome efficacy (KQs 1, 4): <3 month followup for efficacy trials, observational studies Harms (KQs 3, 5): no minimum duration for treatment harms; case series, case reports; n<1000 (KQ 5 only)
Language	***Include***	English only
	Exclude	Non-English languages

Abbreviations: ADL = activities of daily life; CAS = Caregiver Activity Survey; CCT = controlled clinical trial; CSF = cerebrospinal fluid; CT = computed tomography; DHEA = dehydroepiandrosterone; FDA = Food and Drug Administration; HRQL = health-related quality of life; IADL = instumental activities of daily life; KQ = key question; MCI = mild cognitive impaiment; NPV = negative predictive value; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; PET = positron emission tomography; PPV = positive predictive value; RCT = randomized, controlled trial; SMC = subjective memory complaints.

Appendix A. Detailed Methods

Table 3. Quality Rating Criteria

Design	USPSTF quality rating criteria[47]	NICE methodology checklists[48]	QUADAS Tool[49]
Systematic reviews and meta-analyses	• Comprehensiveness of sources considered/search strategy used • Standard appraisal of included studies • Validity of conclusions • Recency and relevance are especially important for systematic reviews	• Study addresses an appropriate and clearly focused question • Description of the methodology used is included • Literature search is sufficiently rigorous to identify all the relevant studies • Study quality is assessed and taken into account • There are enough similarities between the studies selected to make combining them reasonable	Not applicable
Case-control studies	• Accurate ascertainment of cases • Nonbiased selection of cases/controls with exclusion criteria applied equally to both • Response rate • Diagnostic testing procedures applied equally to each group • Measurement of exposure accurate and applied equally to each group • Appropriate attention to potential confounding variables	• Study addresses an appropriate and clearly focused question • Cases and controls are taken from comparable populations • Same exclusion criteria are used for both cases and controls • Percentage of each group (cases and controls) that participated in the study is reported • Comparison is made between participants and non-participants to establish their similarities or differences • Cases are clearly defined and differentiated from controls • Its is clearly established that controls are non-cases • Measures are taken to prevent knowledge of primary exposure influencing case ascertainment • Exposure status is measured in a standard, valid and reliable way • Main potential confounders are identified and taken into account in the design and analysis • Confidence intervals are provided	Not applicable
Randomized controlled trials (RCTs)	• Initial assembly of comparable groups employs adequate randomization, including first concealment and whether potential confounders were distributed equally among groups • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to follow-up or overall high loss to follow-up • Measurements are equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered	• Study addresses an appropriate and clearly focused question • Assignment of subjects to treatment groups is randomized • Adequate concealment method is used • Subjects and investigators are kept 'blind' about treatment allocation • Treatment and control groups are similar at the start of the trial • Only difference between groups is the treatment under investigation • All relevant outcomes are measured in a standard, valid and reliable way • Percentage of individuals or clusters recruited into each treatment arm of the study who dropped out before the study was completed is reported • All subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis) • When the study is carried out at more than one site, results are comparable for all sites	Not applicable

Appendix A. Detailed Methods

Design	USPSTF quality rating criteria[47]	NICE methodology checklists[48]	QUADAS Tool[49]
Cohort studies	• Initial assembly of comparable groups employs consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to follow-up or overall high loss to follow-up • Measurements: equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered	• Study addresses an appropriate and clearly focused question • Two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation • Study indicates how many of the people asked to take part did so, in each of the groups being studied • Likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis • Percentage of individuals or clusters recruited into each arm of the study who dropped out before the study was completed is reported • Comparison is made between full participants and those lost to follow-up, by exposure status • Outcomes are clearly defined • Assessment of outcome is made blind to exposure status • When blinding is not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome • Measure of assessment of exposure is reliable • Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable • Exposure level or prognostic factor is assessed more than once • Main potential confounders are identified and taken into account in the design and analysis • Confidence intervals are provided	Not applicable

Appendix A. Detailed Methods

Design	USPSTF quality rating criteria[47]	NICE methodology checklists[48]	QUADAS Tool[49]
Diagnostic accuracy studies	• Screening test relevant, available for primary care, adequately described • Study uses a credible reference standard, performed regardless of test results • Reference standard interpreted independently of screening test • Handles indeterminate result in a reasonable manner • Spectrum of patients included in study • Sample size • Administration of reliable screening test	• Nature of the test being studied is clearly specified • Test is compared with an appropriate gold standard • Where no gold standard exists, a validated reference standard is used as a comparator • Patients for testing are selected either as a consecutive series or randomly, from a clearly defined study population • Test and gold standard are measured independently (blind) of each other • Test and gold standard are applied as close together in time as possible • Results are reported for all patients that are entered into the study • A pre-diagnosis is made and reported	• Spectrum of patients is representative of the patients who will receive the test in practice • Selection criteria are clearly described • Reference standard is likely to correctly classify the target condition • Time period between the reference standard and the index test is short enough to be reasonably sure that the target condition did not change between the two tests • Whole sample or a random selection of the sample receives verification using a reference standard of diagnosis • Patients receive the same reference standard regardless of the index test result • Reference standard is independent of the index test • Execution of the index test is described in sufficient detail to permit replication of the test • Execution of the reference standard is described in sufficient detail to permit its replication • Index test results are interpreted without knowledge of the results of the reference standard • Reference standard results are interpreted without knowledge of the results of the index test • Same clinical data is available when test results are interpreted as would be available when the test is used in practice • Uninterpretable/intermediate test results are reported • Withdrawals from the study are explained

Appendix B. Excluded Studies

Exclusion Criteria:

CODE	DEFINITION
KQ	Key Question
E1	Study relevance
E1b	Study design: Not an RCT, CCT, or SER (KQ1, 4); Good quality systematic reviews, diagnostic accuracy studies (KQ2); or good quality systematic reviews, RCT/CCT, prospective observational studies for efficacy, retrospective and case-control studies for harms (KQ3,5)
E2b	Study design: Follow up from baseline <3 months (12 weeks) **[Does not apply to harms trials (KQ3,5)]**
E2d	Study design: Case control (only applies to screening trials)
E2e	Study design: n<1000 (only applies to treatment harms trials)
E3a	Setting: Not a country with a very high HDL ranking
E3b	Setting: Hospitals, intermediate care facilities (ICF), skilled nursing facilities, rehabilitation facilities, sub-acute care facilities, emergency departments
E3c	Setting: Unrepresentative Settings (memory clinic, ADRC, referred population setting where the prevalence of dementia is not similar to the general population
E4a	Population: Adults < 65 years or average age < 65 years
E4b	Population: Populations exclusively with HIV/AIDS, Down's syndrome, post-traumatic brain injuries, Parkinson's Disease, stroke, and vitamin deficiency
E4c	Population: Adults with severe dementia
E4d	Population: Professional caregiver (formally or professionally trained, paid salary)
E5	No Relevant Outcomes
E6a	Intervention (Screening): Instruments > 10 min for clinician administration or > 20 min for self-administration; biomarkers (CSF, plasma, urine) or imaging (CT, MRI, PET)
E6b, E6c	Intervention (Treatment): Not one of the specified interventions
E7a	Poor Study Quality: High or differential attrition
E7b	Poor Study Quality: Does not use a reference standard
E7c	Poor Study Quality: Other quality issue
E8	Part of an included SER

1. Study links exercise, improved mental ability. Geriatrics 1986;41(3):24. PMID: None. **KQ4E1b, KQ5E1b.**
2. At-home Alzheimer's test may do more harm than good. Health News 2003 Sep;9(9):7. PMID: 14584472. **KQ3E2a.**
3. Aarsland D, Ballard C, Walker Z, et al. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. Lancet Neurol 2009 Jul;8(7):613-8. PMID: 19520613. **KQ4E4b, KQ5E4b.**
4. Adam S, Van der LM, Ivanoiu A, et al. Optimization of encoding specificity for the diagnosis of early AD: the RI-48 task. J Clin Exp Neuropsychol 2007 Jul;29(5):477-87. PMID: 17564913. **KQ2E3c, KQ3E3c.**
5. ADAPT Research Group, Lyketsos CG, Breitner JC, et al. Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. Neurology 2007 May 22;68(21):1800-8. PMID: 17460158. **KQ4E1b, KQ5E1b.**
6. ADAPT Research Group, Martin BK, Szekely C, et al. Cognitive function over time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): results of a randomized, controlled trial of naproxen and celecoxib. Arch Neurol 2008 Jul;65(7):896-905. PMID: 18474729. **KQ4E1b, KQ5E1b.**
7. ADAPT Research Group, Meinert CL, McCaffrey LD, et al. Alzheimer's Disease Anti-inflammatory Prevention Trial: design, methods, and baseline results. Alzheimers Dement 2009 Mar;5(2):93-104. PMID: 19328435. **KQ4E1b, KQ5E1b.**
8. Agid Y, Dubois B, Anand R, et al. Efficacy and tolerability of rivastigmine in patients with dementia of the Alzheimer type. Curr Ther Res Clin Exp 1998;59:837-45. PMID: None. **KQ4E8, KQ5E8.**
9. Aguglia E, Onor ML, Saina M, et al. An open-label, comparative study of rivastigmine, donepezil and galantamine in a real-world setting. Curr Med Res Opin 2004 Nov;20(11):1747-52. PMID: 15537474.

KQ4E2a, KQ5E2e.
10. Aguirre E, Spector A, Hoe J, et al. Maintenance Cognitive Stimulation Therapy (CST) for dementia: a single-blind, multi-centre, randomized controlled trial of Maintenance CST vs. CST for dementia. Trials 2010;11:46. PMID: 20426866. **KQ4E2b, KQ5E2b.**
11. Ahmed S, De JC, Wilcock G. A comparison of screening tools for the assessment of mild cognitive impairment: preliminary findings. Neurocase 2012;18(4):336-51. PMID: 22044211. **KQ2E2d.**
12. Ainslie NK, Murden RA. Effect of education on the clock-drawing dementia screen in non-demented elderly persons. J Am Geriatr Soc 1993 Mar;41(3):249-52. PMID: 8440847. **KQ2E3c.**
13. Aisen PS. Anti-inflammatory therapy for Alzheimer's disease: implications of the prednisone trial. Acta Neurol Scand 2000;Suppl 176:85-9. PMID: 11261810. **KQ4E6c, KQ5E6c.**
14. Aisen PS, Schmeidler J, Pasinetti GM. Randomized pilot study of nimesulide treatment in Alzheimer's disease. Neurology 2002 Apr 9;58(7):1050-4. PMID: 11940691. **KQ4E6c, KQ5E6c.**
15. Aisen PS, Thal LJ, Ferris SH, et al. Rofecoxib in patients with mild cognitive impairment: further analyses of data from a randomized, double-blind, trial. Current Alzheimer Research 2008 Feb;5(1):73-82. PMID: 18288935. **KQ4E6c, KQ5E6c.**
16. Akkerman RL, Ostwald SK. Reducing anxiety in Alzheimer's disease family caregivers: the effectiveness of a nine-week cognitive-behavioral intervention. Am J Alzheimers Dis Other Demen 2004 Mar;19(2):117-23. PMID: 15106393. **KQ4E7c, KQ5E7c.**
17. Albert M, Smith LA, Scherr PA, et al. Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. Int J Neurosci 1991 Apr;57(3-4):167-78. PMID: 1938160. **KQ2E7c.**
18. Alessi CA, Schnelle JF, MacRae PG, et al. Does physical activity improve sleep in impaired nursing home residents? J Am Geriatr Soc 1995 Oct;43(10):1098-102. PMID: 7560698. **KQ4E3b, KQ5E3b.**
19. Alessi CA, Yoon EJ, Schnelle JF, et al. A randomized trial of a combined physical activity and environmental intervention in nursing home residents: do sleep and agitation improve? J Am Geriatr Soc 1999 Jul;47(7):784-91. PMID: 10404920. **KQ4E3b, KQ5E3b.**
20. Alexopoulos GS, Mattis S. Diagnosing cognitive dysfunction in the elderly: primary screening tests. Geriatrics 1991;46(12):33-8. PMID: 1743529. **KQ2E2a.**
21. Anand R, Messina J, Hartman R. Dose-response effect of rivastigmine in the treatment of Alzheimer's disease. Int J Geriatric Psychopharmacol 2000;2:68-72. PMID: None. **KQ4E5, KQ5E5.**
22. Ancoli-Israel S, Amatniek J, Ascher S, et al. Effects of galantamine versus donepezil on sleep in patients with mild to moderate Alzheimer disease and their caregivers: a double-blind, head-to-head, randomized pilot study. Alzheimer Dis Assoc Disord 2005 Oct;19(4):240-5. PMID: 16327351. **KQ4E2b, KQ5E2e.**
23. Anderson-Hanley C, Arciero PJ, Brickman AM, et al. Exergaming and older adult cognition: A cluster randomized clinical trial. Am J Prev Med 2012;42(2):109-19. PMID: 22261206. **KQ4E2b, KQ5E2b.**
24. Anderson C, Teo K, Gao P, et al. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. Lancet Neurol 2011 Jan;10(1):43-53. PMID: 20980201. **KQ4E1b, KQ5E1b.**
25. Andreeva VA, Kesse-Guyot E, Barberger-Gateau P, et al. Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL.OM3 randomized trial. Am J Clin Nutr 2011 Jul;94(1):278-86. PMID: 21593490. **KQ4E1b, KQ5E1b.**
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27. Aprahamian I, Martinelli JE, Cecato J, et al. Screening for Alzheimer's disease among illiterate elderly: accuracy analysis for multiple instruments. J Alzheimers Dis 2011;26(2):221-9. PMID: 21593559. **KQ2E3a.**
28. Arkin SM. Student-led exercise sessions yield significant fitness gains for Alzheimer's patients. Am J Alzheimers Dis Other Demen 2003;18(3):159-70. PMID: 12811991. **KQ4E2a, KQ5E2a.**

29. Artero S, Ritchie K. The detection of mild cognitive impairment in the general practice setting. Aging Ment Health 2003 Jul;7(4):251-8. PMID: 12888436. **KQ2E1.**
30. Articus K, Baier M, Tracik F, et al. A 24-week, multicentre, open evaluation of the clinical effectiveness of the rivastigmine patch in patients with probable Alzheimer's disease. Int J Clin Pract 2011 Jul;65(7):790-6. PMID: 21645184. **KQ5E2e.**
31. Ashendorf L, Jefferson AL, O'Connor MK, et al. Trail Making Test errors in normal aging, mild cognitive impairment, and dementia. Arch Clin Neuropsychol 2008 Mar;23(2):129-37. PMID: 18178372. **KQ2E2d.**
32. Ashford JW, Adamson M, Beale T, et al. MR spectroscopy for assessment of memantine treatment in mild to moderate Alzheimer dementia. J Alzheimers Dis 2011;26:Suppl-6. PMID: 21971472. **KQ4E7c, KQ5E7c.**
33. Assal F, Allali G, Kressig RW, et al. Galantamine improves gait performance in patients with Alzheimer's disease. J Am Geriatr Soc 2008 May;56(5):946-7. PMID: 18454755. **KQ4E2a, KQ5E5.**
34. Asthana S, Baker LD, Craft S, et al. High-dose estradiol improves cognition for women with AD: results of a randomized study. Neurology 2001 Aug 28;57(4):605-12. PMID: 11524467. **KQ4E2c, KQ5E2c.**
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36. Au A, Li S, Lee K, et al. The coping with caregiving group program for Chinese caregivers of patients with Alzheimer's disease in Hong Kong. Patient Educ Couns 2010 Feb;78(2):256-60. PMID: 19619974. **KQ4E7c, KQ5E7c.**
37. Auriacombe S, Pere JJ, Loria-Kanza Y, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease who failed to benefit from treatment with donepezil. Curr Med Res Opin 2002;18(3):129-38. PMID: 12094822. **KQ4E2a, KQ5E2e.**
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41. Babins L, Slater ME, Whitehead V, et al. Can an 18-point clock-drawing scoring system predict dementia in elderly individuals with mild cognitive impairment? J Clin Exp Neuropsychol 2008 Feb;30(2):173-86. PMID: 18938669. **KQ2E3c.**
42. Bachynsky J, McCracken P, Lier D, et al. Propentofylline treatment for Alzheimer disease and vascular dementia: an economic evaluation based on functional abilities. Alzheimer Dis Assoc Disord 2000 Apr;14(2):102-11. PMID: 10850749. **KQ4E6c, KQ5E6c.**
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44. Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol 2010 Jan;67(1):71-9. PMID: 20065132. **KQ5E5.**
45. Bakker TJ, Duivenvoorden HJ, van der LJ, et al. Integrative psychotherapeutic nursing home program to reduce multiple psychiatric symptoms of cognitively impaired patients and caregiver burden: randomized controlled trial. Am J Geriatr Psychiatry 2011 Jun;19(6):507-20. PMID: 20808147. **KQ4E3b, KQ5E3b.**
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Appendix C. Excluded Treatments

Treatment Category	Drug Name/Type
Drugs for symptom management	Anti-depressants (all)
	Anti-epileptics (all)
	Anti-psychotics (all)
	Nutritional supplements to prevent weight loss (all)
	Ondansetron
Cholinesterase inhibitors not FDA-approved	Eptastigmine
	Metrifonate
	Physostigmine
	Velnacrine
Other drugs not FDA-approved for the treatment of cognitive impairment	Almitrine/raubasine
	Amitriptyline
	Ateroid
	Cerebrolysin
	Choro-San
	Choto-San
	Citicoline
	Cyclandelate
	Denbufylline
	Desferrioxamine
	Ergokryptine (CMB 36-733)
	Ergokryptine (Dek)
	Glycosaminoglycan Polysulfate
	Hydergine
	Hydroxychloroquine
	Idebenone
	Linopirdine
	LU25
	Mifepristone
	Monosialotetrahexosylganglioside (GM-1)
	N-Acetylcysteine
	Naftidrofuryl
	Nicergoline
	Nimesulide
	Nootropic
	ORG 2766
	Oxiracetam
	Piracetam
	Posatirelin
	Prednisone
	Propentofylline
	Reactivan
	Rosiglitozone/pioglitozone
	Sabeluzole
	Selegiline
	Silymarin + Tacrine
	Sulodexide
	Sulphomucopolysaccharides
NSAID not FDA-approved	Rofecoxib
Herbal drugs and supplements	Anapsos
	Curcumin
	Dehydroepiandrosterone (DHEA)
	Ginko Biloba
	Huperzine (herbal cholinesterase inhibitor)
	L-carnitine
	Phosphatidylserine
	Alpha lipoic acid
Experimental drug therapies	Anti-amyloids
Non-pharmacologic therapies	Light therapy

Appendix C. Excluded Treatments

Treatment Category	Drug Name/Type
	Multi-sensory stimulation (MSS) or snoezelen
	Music therapy
	Night-time home monitoring systems
	Peripheral electrical stimulation
	Pet therapy
	Medical foods
	Nutritional interventions

Abbreviations: MSS = multisensory stimulation; DHEA = dehydroepiandrosterone.

Appendix D. Abbreviated Evidence Tables for Key Question 2

Table 1. Study Characteristics and Outcomes for Dementia Screening (Dementia vs. MCI/Normal), Very Brief Instruments

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Ball, 2001[50] Fair	CDT§	1-3	170 53	≥65 y Female Community	76.3 100 13.6	9	Subset	NR	67 (NR††)	69 (NR††)	NR††	NR††	NR
Del Ser, 2006[51] Fair	CDT (Spanish)	1-3	527 416	≥65 y Community	79 51.7 63% <Primary School	11.5	All	NR	97.9 (88.9, 100.0**)	80.7 (76.3, 84.6**)	39.8 (30.9, 49.3**)	99.7 (98.1, 100.0**)	92.7 (NR)
Fuchs, 2011[52] Fair	CDT (German)	1-3	423 423	75-89 y PC	82.4 68.4 62.2% "Low" level	5.0	All	NR	89.5 (75.7, 100.0)	83.7 (80.1, 87.3)	55.6 (38.1, 72.1)	99.7 (98.6, 100)	85.6 (73.3, 97.8)
Grober, 2008[53] Good	CDT	1-3	318 318	≥65 y non-Hispanic White or Black PC	78.7 83 12.6	17.6	All	13	70 (39, 100)	71 (54, 94)	33.9 (25.4, 43.3)	91.6 (86.9, 95.1)	NR
Kirby, 2001[54] Fair	CDT	1-3	648 648	≥65 y PC	75.0 NR 10.8	6.3	All	<6	76 (60, 88*)	81 (77, 84*)	20.8* (14.6, 28.2*)	98.0* (96.4, 99.0*)	NR
Lavery, 2007[55] Fair	CDT	1-3	1107 339	≥65 y PC	77.5 68.7 66.8% ≥12 y	9.7	Subset	NR	NR	NR	NR††	NR††	79.3 (NR)

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Wolf-Klein, 1989[56] Good	CDT	1-3	325 312	Geriatric health center	76.8 70.5 NR	47.1	All	NR	75.2* (66.5, 82.6*)	94.2* (89.9, 97.1*)	89.2* (81.5, 94.5*)	85.7* (80.2, 90.2*)	NR
Borson, 2006[57] Fair	Mini-cog (primary language spoken)	3-4	371 371	Community	NR NR NR	40.2	All	2/3	96.8* (92.6, 98.9*)	71.4* (64.9, 77.3*)	70.6* (64.0, 76.7*)	96.9* (92.9, 99.0*)	NR
Fuchs, 2011[52] Fair	Mini-cog (German)	3-4	423 423	75-89 y PC	82.4 68.4 62.2% "Low" level	5.0	All	NR	100.0 (82.4, 100.0)	85.2 (81.4, 88.4)	26.3** (17.0, 37.3**)	100.0** (98.9, 100.0**)	95.6 (93.1, 98.2)
Holsinger, 2012[58]	Mini-cog	3-4	639 630	≥65 y PC	74.8 7.1 13.0	3.3	All	2/3	76 (54, 90)	73 (69, 76)	8.9** (5.2, 14.0**)	98.9** (97.4, 99.6**)	NR
Kaufer, 2008[59] Fair	Mini-cog	3-4	146 146	≥65 y Residential care/assisted living	83.4 79 Majority with ≥HS	38	All	0	87 (76, 95)	54 (43, 64)	53 (43, 64**)	88 (76, 95**)	70.6
Buschke, 1999[60] Fair	Memory Impairment Screen (MIS)	4	483 483	≥65 y Senior centers; PC	79.5 64 12.1	10.4	All	4	80 (66, 90**)	96 (94, 98**)	70.2** (56.6, 81.6**)	97.7** (95.7, 98.9**)	94 (NR)

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Grober, 2008[53] Good	MIS	4	318 318	≥65 y non-Hispanic White or Black PC	78.7 83 12.6	17.6	All	4	76 (42, 100)	73 (56, 96)	37.7** (28.8, 47.3**)	93.6** (89.4, 96.6**)	NR
Holsinger, 2012[58]	MIS	4	639 630	≥65 y PC	74.8 7.1 13.0	3.3	All	4/5	43 (24, 64)	93 (90, 95)	17.3** (8.2, 30.3**)	97.9** (96.4, 98.9**)	NR
Kuslansky, 2002[61] Fair	MIS	4	240 240	≥70 y PC	78.7 64.1 12.5	11.7	All	4	86 (67, 96**)	97 (94, 99**)	80.0 (61.4, 92.3**)	98.1** (95.2, 99.5**)	93 (NR)
Lipton, 2003[62] Fair	Memory Impairment Screen by telephone (MIS-T)	4	300 300	≥65 y PC	79.3 66.0 12.8	9	Subset	4	78 (58, 91**)	93 (89, 96**)	52 (36.1, 68.5**)	97.7** (95.1, 99.2**)	92 (NR)
Del Ser, 2006[51] Fair	Short Portable Mental Status Questionnaire (SPMSQ) (Spanish)	3-4	527 416	≥65 y Community	79 51.7 63% <Primary School	11.5	All	NR	95.8 (85.8, 99.5**)	88.5 (84.9, 91.7**)	52.2 (41.4, 63.0**)	99.3 (97.8, 99.9**)	97.8 (NR)
Erkinjuntti, 1987[63] Fair	SPMSQ (Finnish)	3-4	119 119	≥65 y Community	73 65 85% ≤Grade school	2.5	All	7/8	100 (29, 100**)	100 (97, 100**)	100 (29.2, 100**)	100 (96.9, 100**)	NR

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Fillenbaum, 1990[64] Fair	SPMSQ	3-4	164 164	≥65 y Community	NR 57.9 NR	16.4	All	NR	92.3* (74.9, 99.1*)	90.2* (83.9, 94.7*)	64.9* (47.5, 79.8*)	98.4* (94.2, 99.8*)	NR
Hooijer, 1992[65] Fair	SPMSQ (Dutch)	3-4	358 358	Older adults PC	NR NR NR	3.6	All	7/8	100 (75.3, 100**)	96.8 (94.4, 98.4**)	54.2 (32.8, 74.5**)	100.0** (98.9, 100.0**)	NR
Fillenbaum, 1990[64] Fair	Mental Status Questionnaire (MSQ)	4	164 164	≥65 y Community	NR 57.9 NR	16.4	All	7/8	100.0* (86.8, 100.0*)	83.5* (76.0, 89.3*)	54.2* (39.2, 68.6*)	100.0* (96.7, 100.0*)	NR
Hooijer, 1992[65] Fair	MSQ (Dutch)	4	358 358	Older adults PC	NR NR NR	3.6	All	7/8	92.3 (64.0, 99.8**)	98.3 (96.3, 99.4**)	66.7 (41.0, 86.7**)	99.7** (98.4, 100.0**)	NR
Del Ser, 2006[51] Fair	Verbal fluency – category (Spanish)	1-2	527 416	≥65 y Community	79 51.7 63% <Primary School	11.5	All	NR	97.9 (88.9, 100.0**)	83.9 (79.8, 87.6**)	44.3 (34.7, 54.3)**	99.6** (98.2, 100.0**)	97.5 (NR)
Fuchs, 2011[52] Fair	Verbal fluency – animals (German)	1-2	423 423	75-89 y PC	82.4 68.4 62.2% "Low" level	5.0	All	≤12	89.5 (75.7, 100.0)	88.3 (85.1, 91.4)	26.6 (15.7, 37.4)	99.4 (98.7, 100.0)	91.8 (83.3, 100.2)

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Grober, 2008[53] Good	Verbal fluency – animals	1-2	318 318	≥65 y non-Hispanic White or Black PC	78.7 83 12.6	17.6	All	12 14	73 (41, 100) 88 (40, 100)	62 (48, 80) 43 (33, 55)	38.1** (28.5, 48.6**)	91.4** (86.9, 94.7**)	NR
Heun, 1998[66] Fair	Verbal fluency – animals (German)	1-2	291 287	60-100 y Community	76.6 59.9 9.5	12.9	All	≤14	81 (65, 92**)	83 (78, 87**)	41.1** (29.7, 53.2**)	96.7** (93.4, 98.7**)	88.5 (82.8, 94.2)
Lavery, 2007[55] Fair	Verbal fluency – animals	1-2	1107 339	≥65 y PC	77.5 68.7 66.8% ≥12 y	9.7	Subset	NR	NR	NR	NR	NR	80.8 (NR)
Heun, 1998[66] Fair	Verbal fluency – first names (German)	1-2	291 287	60-100 y Community	76.6 59.9 9.5	12.9	All	≤14	78 (62, 90**)	85 (80, 89**)	43.3** (31.2, 56.0**)	96.4** (93.0, 98.4**)	87.9 (82.6, 93.2)
Lavery, 2007[55] Fair	Verbal fluency – initial letter	1-2	1107 339	≥65 y PC	77.5 68.7 66.8% ≥12 y	9.7	Subset	NR	NR	NR	NR	NR	78.7 (NR)

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Lipton, 2003[62] Fair	Category Fluency Telephone – animals and fruits	3	300 300	≥65 y PC	79.3 66.0 12.8	9	Subset	13 15 19	37 (19, 58**) 57 (35, 75**) 68 (46, 83**)	97 (94, 99**) 94 (91, 97**) 88 (83, 92**)	55.6** (30.8, 78.5**) 48.4** (30.2, 66.9**) 35.3** (22.4, 49.9**)	94.0** (90.5, 96.5**) 95.5** (92.3, 97.7**) 96.4** (93.3, 98.3**)	89 (NR)
Holsinger, 2012[58]	Memory Function 2 (MF-2)	1.5	639 630	≥65 y PC	74.8 7.1 13.0	3.3	All	Both yes	38 (20, 60)	87 (84, 89)	9.2** (4.1, 17.3**)	97.6** (95.9, 98.7**)	NR
Fuchs, 2011[52] Fair	Subjective memory impairment (German)	1-2	423 423	75-89 y PC	82.4 68.4 62.2% "Low" level	5.0	All	NR	89.5 (75.7, 100.0)	45.8 (40.9, 50.6)	7.3 (3.9, 10.6)	98.9 (97.4, 100.0)	NR
Callahan, 2002[67] Fair	6-item screener	1-2	2212 344	≥65 y Black Community	74.4 59.4 10.4	4.3	Subset	≥3	88.7 (59.5, 98.3**)	88.0 (84.2, 91.4**)	25.0** (14.0, 39.0**)	99.3** (97.6, 99.9**)	95 (NR)
Fong, 2011[68] Fair	Sweet 16	1-3	709 709	≥70 y Community	78.8 60 NR	1.2	All	<14	99 (97, 100)	72 (68, 77)	33 (28, 39)	100 (99, 100)	97 (NR)
Ball, 2001[50] Fair	Short Blessed Test (SBT)	2	170 53	≥65 y Female Community	76.3 100 13.6	9	Subset	>8	40 (NR††)	89 (NR††)	67 (NR††)	87 (NR††)	NR

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Lavery, 2007[55] Fair	Trail making A	1-2	1107 339	≥65 y PC	77.5 68.7 66.8% ≥12 y	9.7	Subset	NR	NR	NR	NR	NR	76.4 (NR)
Lavery, 2007[55] Fair	Trail making B	2-4	1107 339	≥65 y PC	77.5 68.7 66.8% ≥12 y	9.7	Subset	NR	NR	NR	NR	NR	86.8 (NR)
Heun, 1998[66] Fair	Trail making test (assume A and B) (German)	3-6	291 287	60-100 y Community	76.6 59.9 9.5	12.9	All	≤40	81 (65, 92**)	71 (65, 76**)	29.1** (20.6, 38.9**)	96.2** (92.4, 98.5**)	83.6 (75.6, 91.6)
Grober, 2008[53] Good	Oral Trails	4-6‡	318 318	≥65 y non-Hispanic White or Black PC	78.7 83 12.6	17.6	All	2	60 (33, 100)	72 (55, 95)	31.8** (23.1, 41.5**)	89.6** (84.6, 93.4**)	NR
Kuslansky, 2002[61] Fair	3-Word Memory Test	3	240 240	≥70 y PC	78.7 64.1 12.5	11.7	All	NR	65 (44, 81**)	85 (79, 89**)	37 (22.9, 50.8**)	94.7** (90.5, 97.5**)	80 (NR)
Brodaty, 2002[69] Fair	General Practitioner Assessment of Cognition (GPCOG)	4-5	283 202	50-74 y(with memory problem) or ≥75 y PC	79.6 59.4 55.8% >8 y	29	All	10/11	82 (72, 89**)	83 (77, 88**)	67 (56, 75**)	92 (87, 95**)	91 (86-95)

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Fuchs, 2011[52] Fair	Visual Association (VAT) (German)	4-6	423 423	75-89 y PC	82.4 68.4 62.2% "Low" level	5.0	All	7/8	95.2 (86.1, 100.0)	96.0 (94.1, 97.9)	55.6 (39.3, 71.8)	99.7 (99.2, 100.0)	98.1 (96.3, 99.9)
Heun, 1998[66] Fair	Repeated animal names (German)	<5‡	291 287	60-100 y Community	76.6 59.9 9.5	12.9	All	≤1	31 (16, 47**)	76 (70, 81**)	15.5** (8.0, 26.0**)	88.0** (82.9, 92.0**)	53.3 (42.3, 64.3)
Lavery, 2007[55] Fair	Hopkins Verbal Learning Test (HVLT) Immediate recall	<5‡	1107 339	≥65 y PC	77.5 68.7 66.8% ≥12 y	9.7	Subset	NR	NR	NR	NR	NR	90.6 (NR)
Juva, 1997[70] Fair	Katz ADL (Finnish)	≤5‡	656 656	Born in 1904, 1909, or 1914 Community	79.7 73.0 74.4% <HS	14.2	Subset	>1	81 (69, 90*)	83 (79, 87*)	42 (33, 52*)	96.6* (94.0, 98.3*)	90 (80, 94)
Juva, 1997[70] Fair	Lawton IADL (Finnish)	≤5‡	656 656	Born in 1904, 1909, or 1914 Community	79.7 73.0 74.4% <HS	14.2	Subset	<5	91 (80, 97*)	86 (80, 88*)	49 (39.8, 60.2*)	98.2* (95.8, 99.4*)	95 (91, 98)
Cruz-Orduna, 2011[71] Fair	Functional Activities Questionnaire (FAQ) (Spanish)	5	160 160	Cognition-related complaint PC	72.4 70 88.8% ≤primary school	9.4	All	8/9	86.67 (59.54, 98.34**)	82.07 (74.84, 87.94**)	33.3 (19.1, 50.2**)	98.4 (94.2, 99.8**)	91 (84, 96)

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Fillenbaum, 1990[64] Fair	Orientation-Memory Concentration (OMC)	5	164 164	≥65 y Community	NR 57.9 NR	16.4	All	NR	100* (86.8, 100*)	57.9* (49.0, 66.4*)	31.7* (21.9, 42.9*)	100* (95.3, 100*)	NR

* Calculated from 2x2 table.
** Calculated using the sensitivity, specificity, and prevalence of dementia.
§ Authors called their test the Clock Completion Test.
† The SASSI includes the MMSE, Verbal Fluency, and Temporal Orientation.
‡ Assumed.
‖ Reported administration times varied, but the IQCODE can be self-administered in less than 20 minutes, so was included.
†† Confidence intervals or PPV/NPV could not be calculated.

Abbreviations: ADL = activities of daily living; CDT = clock drawing test; CI = confidence interval; FAQ = Functional Activities Questionnaire; GPCOG = General Practitioner Assessment of Cognition; HVLT = Hopkins Verbal Learning Test; IADL = instrumental activities of daily living; MF-2 = Memory Function 2; min = minutes; MIS = Memory Impairment Screen; MIS-T = Memory Impairment Screen by telephone; MSQ = Mental Status Questionnaire; N = number; NPV = negative predictive value; NR = not reported; OMC = Orientation-Memory Concentration; PC = primary care; PPV = positive predictive value; SBT = Short Blessed Test; SE = standard error;Sens = sensitivity; Spec = specificity; SPMSQ = Short Portable Mental Status Questionnaire; VAT = Visual Association; y = year.

Appendix D. Abbreviated Evidence Tables for Key Question 2

Table 2. Study Characteristics and Outcomes for Dementia Screening (Dementia vs. MCI/Normal), Brief Instruments

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens. (95% CI or SE)	Spec. (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Brodaty, 2002[69] Fair	Abbreviated Mental Test (AMT)	5-7	283 269	50-74 y (with memory problem) or ≥75 y PC	79.6 59.4 55.8% >8 y	29	All	7/8	42 (31, 53**)	93 (89, 96**)	71 (55.9, 83.1**)	80 (73.9, 84.5**)	78 (71-84)
Hooijer, 1992[65] Fair	AMT (Dutch)	5-7	358 358	Older adults PC	NR NR NR	3.6	All	7/8	92.3 (64.0, 99.8**)	95.4 (92.6, 97.3**)	42.9 (24.5, 62.8**)	99.7** (98.3, 100.0**)	NR
Rait, 2000[72] Fair	AMT	5-7	130 96	≥60 y Jamaican PC	69 50 9	6	All	≥8	100 (54, 100)	83 (76, 91)	28.6** (11.3, 52.2**)	100.0** (95.2, 100.0**)	NR
Rait, 2000[73] Fair	AMT (Bangladeshi, Gujarati, Hindi, Punjabi, Urdu)	5-7	120 101	≥60 y Gujarati or Pakistani PC	69.2 52.5 NR	11	All	6 [Gujarati] 7 [Pak]	100 (16.0, 100) [Gujarati] 100 (66.4, 100) [Pak]	95.0 (85.8, 99.0) [Gujarati] 86.7 (68.4, 95.6) [Pak]	NR††	NR††	NR
Grober, 2008[53] Good	Free and Cued Selective Reminding Test (FCSRT)	<7‡	318 318	≥65 y non-Hispanic White or Black PC	78.7 83 12.6	17.6	All	25	86 (41, 100)	73 (56, 96)	40.3** (31.5, 49.7**)	96.0** (92.2, 98.3**)	NR

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens. (95% CI or SE)	Spec. (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Del Ser, 2006[51] Fair	Total Free and Cued Recall (FCR) (Spanish)	<7‡	527 416	≥65 y Community	79 51.7 63% <Primary School	11.5	All	NR	100 (92.6, 100**)	87.2 (83.4, 90.5**)	50.5 (40.1, 61.0**)	100 (98.9, 100**)	99.4 (NR)
Del Ser, 2006[51] Fair	7 Minute Screen (Spanish)	7	527 416	≥65 y Community	79 51.7 63% <primary School	11.5	All	NR	100 (92.6, 100**)	95.1 (92.4, 97.1**)	78.6 (60.4, 83**)	100 (99, 100**)	99.6 (NR)
Solomon, 2000[74] Fair	7 Minute Screen	7	137 137	≥60 y PC	77.0 67.2 11.8	8.0	Subset	0.3/0.7 [no patients scored between 0.3 & 0.7]	100* (71.5, 100*)	100* (86.8, 100*)	100* (71.5, 100*)	100* (86.8, 100*)	NR
Manly, 2011[75] Fair	Telephone for Cognitive Status (TICS) (English or Spanish)	7-9	377 377	≥65 y PC	81.4 68.2 10.4	14.1	All	≤22	88 (77, 96**)	87 (83, 91**)	51 (41.9, 63.5**)	98 (95.5, 99.2**)	94 (NR)
Lipton, 2003[62] Fair	TICS	7-9	300 300	≥65 y PC	79.3 66.0 12.8	9	Subset	28	74 (54, 89**)	86 (81, 90**)	34 (22.5, 48.1**)	97.1** (94.1, 98.8**)	86 (NR)
Brodaty, 2002[69] Fair	Mini-Mental State Examination (MMSE)	7-10	283 283	50-74 y (with memory problem) or ≥75 y PC	79.6 59.4 55.8% >8 y	29	All	24/25 [23/24 reported in text]	81 (70, 88**)	76 (70, 82**)	57 (48.3, 67.1**)	90 (85.1, 94.5**)	85 (80-90)

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens. (95% CI or SE)	Spec. (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Callahan, 2002[67] Fair	MMSE	7-10	2212 269	≥65 y Black Community	74.4 59.4 10.4	4.3	Subset	≤24	98.4 (78.2, 100**)	83.6 (79.1, 87.4**)	21.1 (12.7, 33.3**)	99.9 (98.7, 100**)	96 (NR)
Cruz-Orduna, 2011[71] Fair	MMSE (Spanish)	7-10	160 160	Cognition-related complaint PC	72.4 70 88.8% ≤primary school	9.4	All	18/19	80.0 (51.9, 95.7**)	86.2 (79.5, 91.4**)	37.5 (21.1, 56.3**)	97.7 (93.3, 99.5**)	89 (82, 95)
Cullen, 2005[76] Fair	MMSE	7-10	1142 1115	≥65 y PC	74.8 68 9.9	3.9	All	<24	90.9 (78.3, 97.5**)	87.1 (85.0, 89.1**)	22.5** (16.6, 29.3**)	99.6** (98.9, 99.9**)	NR
Fillenbaum, 1990[64] Fair	MMSE	7-10	164 164	≥65 y Community	NR 57.9 NR	16.4	All	NR	100* (86.8, 100*)	77.4* (69.4, 84.2*)	46.4* (33, 60.3*)	100* (96.5, 100*)	NR
Fong, 2011[68] Fair	MMSE	7-10	709 709	≥70 y Community	78.8 60 NR	1.2	All	<24	87 (78, 95)	89 (86, 92)	52 (44, 60)	98 (96, 99)	95 (NR)
Gagnon, 1990[77] Fair	MMSE (French)	7-10	2730 2730	≥65 y Community	74.6 59.4 66% ≤primary school	3.7	All	24	100 (96, 100*)	78 (77, 80*)	15.0 (12.4, 17.9*)	100* (99.8, 100*)	NR

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens. (95% CI or SE)	Spec. (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Grut, 1993[78] Fair	MMSE (Swedish)	7-10	1810 668	>74 y Community	NR 76.1 46.1 ≥HS	14.1	Subset	24/25	90 (NR††)	86 (NR††)	57 (NR††)	NR††	NR
Heun, 1998[66] Fair	MMSE (German)	7-10	291 287	60-100 y Community	76.6 59.9 9.5	12.9	All	≤24	92 (78, 98**)	96 (93, 98**)	77.3** (62.2, 88.5**)	98.8** (96.4, 99.7**)	98.8 (88.0, 100)
Hooijer, 1992[65] Fair	MMSE (Dutch)	7-10	358 358	Older adults PC	NR NR NR	3.6	All	23/24	76.9 (46.2, 95.0**)	96.5 (94.0, 98.2**)	45.5 (24.4, 67.8**)	99.1** (97.4, 99.8**)	NR
Jeong, 2004[79] Good	MMSE (Korean)	7-10	235 235?	≥65 y Community	73.5 66.4 1 (median)	19.6	All	18/19	91 (79, 98)	76 (69, 82)	48.3** (37.4, 59.3**)	97.3** (93.2, 99.3**)	89 (2)
Jorm, 1996[80] Fair	MMSE	7-10	144 143	POW/ veteran	72.9 0 NR	NR	All	26/27	67 (NR††)	85 (NR††)	NR††	NR††	81 (5)
Kahle-Wrobleski, 2007[81] Fair	MMSE	7-10	435 435	≥90 y Retirement community	95 74 73% >12 y	36	All	24	85.2** (78.6, 90.4**)	80.7** (75.6, 85.2**)	71.0** (63.9, 77.4**)	90.8** (86.5, 94.1**)	92
Kaufer, 2008[59] Fair	MMSE	7-10	146 146	≥65 y Residential care/ assisted living	83.4 79 Majority with ≥HS	38	All	<27	82 (69, 91)	67 (56, 77)	60 (48, 71.2**)	86 (75.6, 93**)	85.4 (NR)

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens. (95% CI or SE)	Spec. (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Kay, 1985[82] Fair	MMSE	7-10	274 274	≥70 y Community	NR (158 were 70-79, 116 were 80+ 63.5	14.2	All	24/25	84.6 (69.5, 94.1**)	80.8 (75.2, 85.7**)	42.3** (31.2, 54**)	96.9** (93.5, 98.9**)	NR
Kirby, 2001[54] Fair	MMSE	7-10	648 648	≥65 y PC	75.0 NR 10.8	6.3	All	<24	88 (74, 96*)	88 (85, 90*)	32.4* (23.9, 42.0*)	99.1* (97.8, 99.7*)	NR
Lam, 2008[83] Fair	MMSE (Chinese - Cantonese)	7-10	459 459	Community	71.2 54.5 4.8	9.6	All	NR	NR	NR	NR	NR	81.1 (NR)
Lavery, 2007[55] Fair	MMSE	7-10	1107 339	≥65 y PC	77.5 68.7 66.8% ≥12 y	9.7	Subset	≥22	68 (48, 84**)	92 (88, 95**)	45 (29.9, 61.3**)	97 (93.8, 98.5**)	91.2 (NR)
McDowell, 1997[84] Fair	MMSE (English or French)	7-10	1600 1600	≥65 y	80.0 59 8.6	23	Subset	24	63 (58, 68**)	89 (87, 91**)	63.0** (57.9, 68**)	89.0** (87.1, 90.7**)	89 (1.2)
Morales, 1997[85] Fair	MMSE (Spanish)	7-10	257(97 urban, 160 rural) 257	≥65 y (urban) ≥60 y (rural) Community	74.1 61.9 4.9	13.2	Subset	21 [urban] 20 [rural]	73 (39, 94**) [urban] 83 (61, 95**) [rural]	78 (68, 86**) [urban] 74 (66, 81**) [rural]	30(13.8, 50.2**) [urban] 34 (22.2, 48.6**) [rural]	96 (88.0, 99.1**) [urban] 95 (90.5, 99.0**) [rural]	NR

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens. (95% CI or SE)	Spec. (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Rait, 2000[72] Fair	MMSE	7-10	130 96	≥60 y Jamaican PC	69 50 9	6	All	≥27	100 (54, 100)	69 (60, 78)	17.7** (6.8, 34.5**)	100** (94.2, 100**)	NR
Rait, 2000[73] Fair	MMSE (Bangladeshi, Gujarati, Hindi, Punjabi, Urdu)	7-10	120 101	≥60 y Gujarati or Pakistani PC	69.2 52.5 NR	11	All	24 [Gujarati] 27 [Pak]	100 (16.0, 100) [Gujarati] 100 (66.4, 100) [Pak]	95.0 (85.8, 99.0) [Gujarati] 76.7 (57.3, 89.4) [Pak]	NR††	NR††	NR
Reischies, 1997[86] Fair	MMSE (German)	7-10	516 449	≥70 y Community	NR NR NR	19.4	All	24/25	84.1 (74.5, 90.9**)	83.1 (78.9, 86.9**)	54.5** (45.7, 63.1**)	95.6** (92.7, 97.6**)	NR
Scharre, 2010[87] Fair	MMSE	7-10	254 63	>59 y Geriatric outpatient; community; independent and assisted living facilities; senior centers; memory clinic	78 66.7 93.7% ≥HS	33	Subset	26 or less	90 (70, 99**)	88 (74, 96**)	79.2** (57.9, 92.9**)	94.9** (82.7, 99.4**)	94.9 (NR)
Waite, 1998[88] Fair	MMSE	7-10	630 360	≥75 y Community; veterans	83.9 54.8 10	27.5	All	23/24	84 (75, 90**)	88 (84, 92**)	72.8** (63.7, 80.7**)	93.5** (89.7, 96.2**)	93 (NR)

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens. (95% CI or SE)	Spec. (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Reischies, 1997[86] Fair	MMblind (German)	7-10	516 491	≥70 y Community	NR NR NR	20.4	All	17/18	84.9 (76.5, 91.4**)	82.1 (77.9, 85.8**)	54.8** (46.7, 62.8**)	95.5** (92.7, 97.5**)	NR
Markwick, 2012[89] Good	MoCA	10	107 107	MMSE ≥24 NR	76 54 76.6% >12 y	7.5	All	<26	100.0* (63.1, 100.0*)	66.7* (56.3, 76.0*)	20.0* (9.1, 35.7*)	100.0* (94.4, 100.0*)	NR
Waite, 1998[88] Fair	Short Concord Informant Dementia Scale	6-11	630 360	≥75 y Community; veterans	83.9 54.8 10	27.5	All	3/4	83 (74, 90**)	87 (82, 91**)	70.7** (61.5, 78.8**)	93.0** (89.1, 95.9**)	89 (NR)
Del Ser, 2006[51] Fair	Benton's Orientation Test (Spanish)	<7‡	527 416	≥65 y Community	79 51.7 63% <Primary School	11.5	All	NR	95.8 (85.8, 99.5**)	85.5 (81.6, 89.0**)	46.4 (36.4, 56.8**)	99.3 (97.7, 99.9**)	97.0 (NR)
Fillenbaum, 1990[64] Fair	Kendrick Cognitive tests	<7‡	164 164	≥65 y Community	NR 57.9 NR	16.4	All	NR	65.4* (44.3, 82.8*)	94.7* (89.5, 97.9*)	70.8* (48.9, 87.4*)	93.3* (87.7, 96.9*)	NR

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens. (95% CI or SE)	Spec. (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Heun, 1998[66] Fair	Word List Learning (German)	<7‡	291 287	60-100 y Community	76.6 59.9 9.5	12.9	All	≤3 [IR] ≤6 [IRH] ≤1 [IRFA]	82 (65, 92**) [IR] 57 (39, 73**) [IRH] 23 (12, 41**) [RFA]	77 (71, 82**) [IR] 71 (65, 76**) [IRH] 77 (71, 82**) [RFA]	34.1** (24.3, 45**) [IR] 22.3** (14.4, 32.1**) [IRH] 13.4** (6.3, 24.0**) [RFA]	96.5** (92.9, 98.6**) [IR] 91.8** (87, 95.2**) [IRH] 87.3** (82.2, 91.4**) [RFA]	87.1 (81.4, 92.8) [IR] 67.0 (56.2, 77.8) [IRH] 51.5 (40.1, 62.9) [IRFA]
Heun, 1998[66] Fair	Labyrinth Test (German)	<7‡	291 287	60-100 y Community	76.6 59.9 9.5	12.9	All	≤80 [sec] ≤3 [mis]	56 (39, 73**) [sec] 88 (75, 97**) [mis]	84 (79, 88**) [sec] 60 (54, 66**) [mis]	34.4** (22.7. 47.7**) [sec] 24.8** (17.7, 33.0**) [mis]	92.9** (88.8, 95.9**) [sec] 97.4** (93.5, 99.3**) [mis]	72.5 (59.2, 85.8) [sec] 80.2 (71.6, 88.8) [mis]
Lavery, 2007[55] Fair	Rey figure immediate recall	<7‡	1107 339	≥65 y PC	77.5 68.7 66.8% ≥12 y	9.7	Subset	NR	NR	NR	NR	NR	88.7 (NR)
Lavery, 2007[55] Fair	Rey figure copy	<7‡	1107 339	≥65 y PC	77.5 68.7% ≥12 y of education: 66.8	9.7	Subset	NR	NR	NR	NR	NR	79.8 (NR)

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens. (95% CI or SE)	Spec. (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Fuchs, 2011[52] Fair	Immediate recall (German)	<10‡	423 423	75-89 y PC	82.4 68.4 62.2% "Low" level	5.0	All	NR	100.0 (100.0, 100.0)	82.8 (79.0, 86.5)	20.7 (12.2, 29.2)	100.0 (100.0, 100.0)	95.7 (92.7, 98.7)
Kaufer, 2008[59] Fair	Minimum Data Set Cognition Scale (MDS-Cog)	<10‡	146 146	≥65 y Residential care/ assisted living	83.4 79 Majority with ≥HS	38	All	NR	67 (55, 80)	84 (76, 91)	71.2** (56.9, 82.9**)	80.9** (71.4, 88.2**)	78.8 (NR)
Fillenbaum, 1990[64] Fair	Storandt Battery	10	164 164	≥65 y Community	NR 57.9 NR	16.4	All	NR	100* (86.8, 100*)	56.4* (47.5, 65.0*)	31.0* (21.3, 42.0*)	100* (95.2, 100*)	NR

* Calculated from 2x2 table.
** Calculated using the sensitivity, specificity, and prevalence of dementia.
§ Authors called their test the Clock Completion Test.
† The SASSI includes the MMSE, Verbal Fluency, and Temporal Orientation.
‡ Assumed.
†† Confidence intervals or PPV/NPV could not be calculated.

Abbreviations: AMT = Abbreviated Mental Test; AUC = area under the curve; CI = confidence interval; FCR = total free and cued recall; FCSRT = Free and Cued Selective Reminding Test; IR = Immediate Recall; IRFA = Immediate Recognition False Alarm; IRH = Immediate Recognition Hit; MDS-Cog = Minimum Data Set Cognition Scale; mis = mistake; MMSE = Mini-Mental State Examination; N = number; NPV = negative predictive value; NR = not reported; PC = primary care; POW = prisoner of war; PPV = positive predictive value; RFA = Recognition False Alarm; SE = standard error; TICS = Telephone for Cognitive Status; y = year.

Appendix D. Abbreviated Evidence Tables for Key Question 2

Table 3. Study Characteristics and Outcomes for Dementia Screening (Dementia vs. MCI/Normal), Self-Administered Instruments

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Grober, 2008[53] Good	Short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)	NR‖	318 318	≥65 y non-Hispanic White or Black PC	78.7 83 12.6	17.6	All	3.3	81 (41, 100)	80 (59, 100)	46.4** (36.2, 56.8**)	95.0** (91.3, 97.5**)	NR
Jorm, 1996[80] Fair	Short IQCODE	NR‖	144 143	POW/ veterans	72.9 0 NR	NR	All	3.31/ 3.38	75 (NR††)	68 (NR††)	NR††	NR††	77 (6)
Cruz-Orduna, 2011[71] Fair	Full IQCODE (Spanish)	NR‖	160 160	Cognition-related complaint PC	72.4 70 88.8% ≤primary school	9.4	All	3.65/ 3.69	80.00 (51.91, 95.67**)	76.71 (68.80, 83.18**)	26.1 (14.3, 41.1**)	97.4 (92.5, 99.5**)	85 (76, 94)
Morales, 1997[85] Fair	Full IQCODE (Spanish)	NR‖	257(97 urban, 160 rural) 257	≥65 y (urban); ≥60 y (rural) Community	74.1 61.9 4.9	13.2	Subset	3.27 [urban] 3.31 [rural]	82 (48, 98**) [urban] 83 (61, 95**) [rural]	90 (81, 95**) [urban] 83 (76, 89**) [rural]	50.0 (26.0, 74.0**) [urban] 45 (29.9, 61.3**) [rural]	97 (91.2, 99.7**) [urban] 97 (91.6, 99.1**) [rural]	NR
Jorm, 1996[80] Fair	Full IQCODE	NR‖	144 143	POW/ veterans	72.9 0 NR	NR	All	3.27/3.30	79 (NR††)	65 (NR††)	NR††	NR††	77 (6)

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia	Diagnostic Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Tokuhara, 2006[90] Fair	Full IQCODE	NR‖	299 230 (N analyzed unclear)	≥65 y Japanese/ Okinawan PC	74.2 66 12.2	7	All	3.5	87.5 (61.7, 98.5**)	91.1 (86.8, 94.3**)	42.4 (23.1, 56.5**)	99 (96.8, 99.9**)	NR
Swearer, 2002[91] Fair	Cognitive Assessment Screening Test (CAST)	15	46 46	PC; Retirement community	80.6 65 14.4	17	All	<34	88 (47, 100*)	95 (82, 99*)	77.8* (40.0, 97.2*)	97.3* (85.8, 99.9*)	NR
Scharre, 2010[87] Fair	Self-administered Gerocognitive Examination (SAGE)	10-15	254 63	>59 y Geriatric outpatient; community; independent and assisted living facilities; senior centers; memory clinic	78 66.7 93.7% ≥HS	33	Subset	≤14	81 (58, 95**)	88 (74, 96**)	77.3** (54.6, 92.2**)	90.2** (76.9, 97.3**)	90.6 (NR)

* Calculated from 2x2 table.
** Calculated using the sensitivity, specificity, and prevalence of dementia.
§ Authors called their test the Clock Completion Test.
† The SASSI includes the MMSE, Verbal Fluency, and Temporal Orientation.
‡ Assumed.
‖ Reported administration times varied, but the IQCODE can be self-administered in less than 20 minutes, so was included.
†† Confidence intervals or PPV/NPV could not be calculated.

Abbreviations: AUC = area under the curve; CAST = Cognitive Assessment Screening Test; CI = confidence interval; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; NPV = negative predictive value; NR = not reported; PC = primary care; POW = prisoner of war; PPV = positive predictive value; SAGE = Self-administered Gerocognitive Examination; SE = standard error; Y = year.

Appendix D. Abbreviated Evidence Tables for Key Question 2

Table 4. Study Characteristics and Outcomes for Mild Cognitive Impairment Screening (MCI vs. Normal, Dementia Not Included), Very Brief Instruments

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Donnelly, 2008[92] Fair	Clock Drawing Test (CDT)	1-3	100 100	≥65 y PC	77.9 1 12.9	20	>1.0 SD below norm All	1 SD	85 (62, 97)	44 (33, 55)	27 (17, 40)	92 (79, 98)	73 (NR)
Ehreke, 2009[93] Fair	CDT (German)	1-3	3198 3198	≥75 y PC	80.10 65.4 61.8% “low” level	15.0 [orig] 24.6 [mod]	Mayo criteria All	9	58.2 (53.7, 62.7**) [orig] 59.4 (55.9, 62.9**) [mod]	57.3 (55.4, 59.2**) [orig] 59.7 (57.7, 61.7**) [mod	19.4** (17.4, 21.5**) [orig] 32.5** (30.0, 34.9**) [mod]	88.6** (87.1, 90.1**) [orig] 81.9** (80.0, 83.6**) [mod	0.595 (NR) [orig] 0.616 (NR) [mod]

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Ehreke, 2011[94] Fair	CDT (German)	1-3	428 428	≥75 y Community	83.3 73.1 63.5% "low" education	13.6	Int'l Working Group on MCI (Win) All	≥2 (Shu) ≤9 (Ihl and Sun) ≤7 (Rou) ≤15 (Bab) ≤18 (Men) ≤2 (Lin)	76 (63, 86**) [Shu] 69 (56, 81**) [Ihl and Sun] 48 (35, 62**) [Rou] 60 (47, 73**) [Bab] 64 (50, 76**) [Men] 76 (63, 86**) [Lin]	58 (53, 63**) [Shu] 63 (58, 68**) [Ihl and Sun] 79 (74, 83**) [Rou] 70 (65, 75**) [Bab] 70 (65, 75**) [Men] 49 (44, 54**) [Lin]	22.1** (16.6, 28.5**) [Shu] 22.6** (16.7, 29.5**) [Ihl and Sun] 26.4** (18.3, 35.9**) [Rou] 24.0** (17.3, 31.7**) [Bab] 25.0** (18.3, 32.8**) [Men] 18.9** (14.1, 24.5**) [Lin]	93.9** (90.0, 96.6**) [Shu] 92.8** (88.9, 95.7**) [Ihl and Sun] 90.7** (87.0, 93.6**) [Rou] 91.8** (88.0, 94.8**) [Bab] 92.5** (88.8, 95.3**) [Men] 92.8** (88.3, 96.0**) [Lin]	0.676 (Shu) 0.663 (Ihl and Sun) 0.678 (Rou) 0.694 (Bab) 0.689 (Men) 0.642 (Lin)

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Lee, 2008[95] Fair	CDT (Korean)	1-3	465 465	≥60 y Hospital outpatients; community	71.0 63.4 53.1% <primary school	48.2	Mayo criteria All	9/10 [Fre] 6/6.5 [Tod] 7/8 [Rou] 1/2 [CER]	40.7 (34.1, 47.4**) [Fre] 44.4 (37.6, 51.0**) [Tod] 56.4 (49.5, 62.9**) [Rou] 43.0 (36.3, 49.6**) [CER]	83.0 (77.6, 87.5**) [Fre] 81.3 (75.8, 86.0**) [Tod] 71.8 (65.7, 77.4**) [Rou] 85.3 (80.4, 89.7**) [CER]	68.9** (60.3, 76.7**) [Fre] 68.8** (60.5, 76.2**) [Tod] 65.0** (57.8, 71.6**) [Rou] 73.3** (64.9, 80.6**) [CER]	60.1** (54.6, 65.4**) [Fre] 61.1** (55.5, 66.4**) [Tod] 63.8** (57.8, 69.6**) [Rou] 61.7** (56.2, 66.9**) [CER]	0.653 (0.604, 0.701) [Fre] 0.661 (0.613, 0.710) [Tod] 0.669 (0.621, 0.717) [Rou] 0.656 (0.606, 0.706) [CER]
Kaufer, 2008[59] Fair	Mini-cog	3-4	146 91	≥65 y Residential care/assisted living facilities	83.4 79 Majority >HS	83.5	Mayo criteria All	0	50 (38, 62)	73 (42, 92)	90 (77.4, 97.3**)	22 (11.8, 36.6**)	0.617 (NR)
Ayalon, 2011[96] Fair	Single item informant report	1-2	856 441	≥70 y PC	80.3 55.6 11.2	42.0	≥1.5 SD below norm All	>2	81.1 (74.7, 86.5**)	75.3 (69.6, 80.5**)	70.4**£ (63.8, 76.5**)£	84.7**£ (79.3, 89.1**)£	0.85 (0.01)
Li, 2006[97] Fair	Informant Report of Memory Problems (IRMP) (Chinese or English)	1-2	144 125	65-90 y Community; neuro-science clinic	72.7 50.7 4.7	29.6	Mayo criteria and CDR= 0.5 All	NR	NR	NR	NR	NR	0.795 (0.046)

Appendix D. Abbreviated Evidence Tables for Key Question 2

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Donnelly, 2008[92] Fair	Trail Making Test A (TMT-A)	1-2	100 100	≥65 y PC	77.9 1 12.9	20	>1.0 SD below norm All	1 SD	30 (12, 54)	90 (81, 96)	43 (18, 71)	84 (74, 91)	72 (NR)
Donnelly, 2008 [92] Fair	Trail Making Test B (TMT-B)	2-4	100 100	≥65 y PC	77.9 1 12.9	20	>1.0 SD below norm All	1 SD	43 (18, 71)	86 (76, 93)	35 (14, 62)	89 (80, 95)	66 (NR)
Donnelly, 2008[92] Fair	Hopkins Verbal Learning Test (HVLT)	5	100 100	≥65 y PC	77.9 1 12.9	20	>1.0 SD below norm All	1 SD	55 (32, 77)	43 (32, 54)	19 (10, 32)	79 (64, 90)	55 (NR)
Li, 2006[97] Fair	Brief IADL (4IADL) (Chinese or English)	<5‡	144 125	65-90 y Community; neuro-science clinic	72.7 50.7 4.7	29.6	Mayo criteria and CDR= 0.5 All	NR	NR	NR	NR	NR	0.769 (0.045)

* Calculated from 2x2 table.
‡ Assumed.
‖ Reported administration times varied, but the IQCODE can be self-administered in less than 20 minutes, so was included.
†† Confidence intervals could not be calculated.
** Calculated using the sensitivity, specificity, and prevalence of MCI.
£ PPV and NPV reported in the text do not match what was calculated using the sensitivity, specificity, and prevalence of MCI. The numbers presented have been calculated.

Abbreviations: ADL = activities of daily living; AUC = Area Under the Curve ; Bab = Babins ; CAST = Cognitive Assessment Screening Test ; CDT = clock drawing test; CER = CERAD (Consortium to Establish a Registry for Alzheimer's Disease); CI = confidence interval; Fre = Freedman; HVLT = Hopkins Verbal Learning Test; IADL = instrumental activities of daily living; IQCODE = Short Informant Questionnaire on Cognitive Decline in the Elderly ; IRMP = Informant Report of Memory Problems; MCI = Mild Cognitive Impairment; Men = Mendez; mod = modified; N = number; NPV = negative predictive value; NR = not reported; org = orginal; PC = primary care; PPV = positive predictive value; Rou = Rouleau; SAGE = Self-Administered Gerocognitive Examination ; SD = Standard Deviation ; SE = standard error; Sens = sensitivity; Shu = Shuman; Spec = specificity; Sun = Sunderland; TMT = trail making test; Tod = Todd; Win = Winblad; y = year.

Appendix D. Abbreviated Evidence Tables for Key Question 2

Table 5. Study Characteristics and Outcomes for Mild Cognitive Impairment Screening (MCI vs. Normal, Dementia Not Included), Brief Instruments

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Cook, 2009[98] Fair	Telephone interview for Cognitive Impairment Modified (TICS-M)	7-9	71 71	≥65 y Community	74.9 56.3 16.1	23.9	"spirit" of Mayo criteria and CDR=0.5 All	26 31 34	17.6 (3.8, 43.4**) 47.1 (23.0, 72.2**) 82.4 (56.6, 96.2**)	100 (93.4, 100**) 100 (93.4, 100**) 87.0 (75.1, 94.6**)	100.0 (29.2, 100**) 100.0 (63.1, 100**) 66.7 (43, 85.4**)	79.4 (67.9, 88.3**) 85.7 (74.6, 93.3**) 94.0 (83.5, 98.8**)	93.3 (3.2)
Donnelly, 2008[92] Fair	Mini-Mental State Examination (MMSE)	7-10	100 100	≥65 y PC	77.9 1 12.9	20	>1.0 SD below norm All	1 SD	20 (6, 44)	93 (84, 97)	40 (12.74)	82 (73, 89)	72 (NR)
Kaufer, 2008[59] Fair	MMSE	7-10	146 91	≥65 y Residential care/ assisted living facilities	83.4 79 Majority >HS	83.5	Mayo criteria All	<28	47 (36, 59)	73 (45, 92)	90 (76.3, 97.2**)	22 (11.3, 35.3**)	0.666 (NR)
Li, 2006[97] Fair	MMSE (Chinese or English)	7-10	144 125	65-90 y Community; neuro-science clinic	72.7 50.7 4.7	29.6	Mayo criteria and CDR=0.5 All	NR	NR	NR	NR	NR	0.676 (0.051)
McDowell, 1997[84] Fair	MMSE (English or French)	7-10	1600 1232	≥65 y	80.0 59 8.6	39.0	CIND criteria NR Subset	NR	NR	NR	NR	NR	0.77 (0.012)

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Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Rideaux, 2012[99] Fair	MMSE (English or Spanish)	7-10	701 522	≥70 y Community	80.5 55.2 10.3	42.5	≥1.5 SD below norm All	<26 (White) <23 (Black) <25 (Latino)	58 (50, 66**) [White] 67 (53, 80**) [Black] 93 (86, 100) [Latino]	86 (81, 90**) [White] 71 (54, 85**) [Black] 71 (60, 83) [Latino]	72.0** (63.0, 79.9**) [White] 75.0** (59.7, 86.8**) [Black] 93 (64, 87) [Latino]	76.7** (71.1, 81.7**) [White] 62.8** (46.7, 77.0**) [Black] 71 (83, 99) [Latino]	NR
Saxton, 2009[100] Good	MMSE	7-10	524 524	≥60 y PC; Senior community centers	73.3 65.1 13.46	43.5	At least 2 test scores 1-2 SD below norm All	28	45 (39, 52**)	80 (75, 84**)	63.6** (55.7, 71**)	65.5** (60.3, 70.4**)	NR
Scharre, 2010[87] Fair	MMSE	10-15	254 42	>59 y Geriatric outpatient; community; independent and assisted living facilities; senior centers; memory clinic	78 66.7 93.7% ≥HS	50	≥1.5 SD below norm Subset	NR	71 (55, 84**)	90 (70, 99**)	93.8** (79.2, 99.2**)	61.3** (42.2, 78.2**)	0.628

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Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Tariq, 2006[101] Fair	MMSE	7-10	702 620	≥60 y VA	75.3 NR 69.4% ≥HS	29.0	MNCD criteria NR All	28.5 [<HS edu] 29.5 [HS edu+]	60 (45, 74**) [<HS edu] 75 (66, 82**) [HS edu+]	65 (56, 73**) [<HS edu] 48 (42, 54**) [HS edu+]	38 (27.7, 50.2**) [<HS edu] 38 (32.3, 44.5**) [HS edu+]	82 (73.1, 88.4**) [<HS edu] 82 (75.0, 86.9**) [HS edu+]	67.1 (NR) [<HS edu] 64.3 (NR) [HS edu+]
Lee, 2008[102] Fair	Montreal Cognitive Assessment (MoCA) (Korean)	10	196 152	≥60 y Hospital outpatients; community	69.8 64.8 53.1% <primary school	24.3	Mayo criteria All	25/26	100 (91, 100**)	50 (41, 59**)	39.0** (29.1, 49.5**)	100.0** (93.8, 100.0**)	0.94 (0.90-0.98)
Markwick, 2012[89] Good	MoCA	10	107 99	MMSE ≥24 NR	76 54 76.6% >12 y	20.2	Petersen criteria All	<26	80.0* (56.3, 94.3*)	76.0* (65.0, 84.9*)	45.7* (28.8, 63.4*)	93.8* (84.8, 98.3*)	NR
Li, 2006[97] Fair	Immediate Recall (Logical Memory I) (Chinese or English)	<7‡	144 125	65-90 y Community; neuro-science clinic	72.7 50.7 4.7	29.6	Mayo criteria and CDR=0.5 All	NR	NR	NR	NR	NR	0.812 (0.044)
Rideaux, 2012[99] Fair	Fuld Object Memory Evaluation (FOME), abbreviated (English or Spanish)	9	701 522	≥70 y Community	81 55 10.3	42.5	≥1.5 SD below norm All	<21 (White) <22 (Black) <25 (Latino)	55 (50, 60) [White] 65 (55, 75) [Black] 93 (76, 99**) [Latino]	93 (91, 96) [White] 74 (64, 83) [Black] 57 (37, 76**) [Latino]	83 (80, 87) [White] 76 (67, 85) [Black] 67.6** (50.2, 82.0**) [Latino]	80 (75, 84) [White] 62 (52, 72) [Black] 88.9** (65.3, 98.6**) [Latino]	NR

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Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Tariq, 2006[101] Fair	St. Louis University Mental Status Examination (SLUMS)	7	702 620	≥60 y VA	75.3 NR 69.4% ≥ HS	29.0	MNCD criteria NR All	23.5 [<HS edu] 25.5 [HS edu+]	92 (81, 98**) [<HS edu] 95 (89, 98**) [HS edu+]	81 (73, 87**) [<HS edu] 76 (71, 81**) [HS edu+]	64 (51.7, 74.9**) [<HS edu] 62.9**£ (55.8, 69.7**£) [HS edu+]	97 (91.3, 99.0**) [<HS edu] 97.1**£ (94, 98.8**£) [HS edu+]	92.7 (NR) [<HS edu] 94.1 (NR) [HS edu+]

* Calculated from 2x2 table.
‡ Assumed.
‖ Reported administration times varied, but the IQCODE can be self-administered in less than 20 minutes, so was included.
†† Confidence intervals could not be calculated.
** Calculated using the sensitivity, specificity, and prevalence of MCI.
£ PPV and NPV reported in the text do not match what was calculated using the sensitivity, specificity, and prevalence of MCI. The numbers presented have been calculated.

Abbreviations: AUC = area under the curve; CDR = clinical dementia rating; CI = confidence interval; CIND = cognitive impairment, no dementia; edu = education; FOME = Fuld Object Memory Evaluation; HS = high school; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MNCD = mild neurocognitive disorder; N = number; NPV = negative predictive value; NR = not reported; PC = primary care; PPV = positive predictive value; SD = standard deviation; SE = standard error; SLUMS = St. Louis University Mental Status Examination; TICS-M = Telephone interview for Cognitive Impairment Modified; VA = Veterans Affairs; y = year.

Appendix D. Abbreviated Evidence Tables for Key Question 2

Table 6. Study Characteristics and Outcomes for Mild Cognitive Impairment Screening (MCI vs. Normal, Dementia Not Included), Self-Administered Instruments

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Ayalon, 2011[96] Fair	Short Informant Questionnaire IQCODE	NR‖	856 441	≥70 y PC	80.3 55.6 11.2	42.0	≥1.5 SD below norm All	>3	74.8 (67.7, 80.7**)	69.0 (63.1, 74.7**)	63.6**£ (56.9, 70.0**£)	79.0**£ (73.1, 84.2**£)	0.77 (0.02)
Saxton, 2009[100] Good	Computer Assessment of Mild Cognitive Impairment (CAMCI)	NR	524 524	≥60 y PC; Senior community centers	73.3 65.1 13.46	43.5	At least 2 test scores 1-2 SD below norm All	NR	86 (83, 92*)	94 (90, 96*)	91.4* (86.8, 94.7*)	91.1* (87.3, 94.1*)	NR
Scharre, 2010[87] Fair	Self-administered Gerocognitive Examination (SAGE)	10-15	254 42	>59 y Geriatric outpatient; community; independent and assisted living facilities; senior centers; memory clinic	78 66.7 93.7% ≥HS	50	≥1.5 SD below norm Subset	16/17	79 (63, 90**)	95 (76, 100**)	97.1** (84.7, 99.9**)	69.0** (49.2, 84.7**)	0.850

* Calculated from 2x2 table.
‡ Assumed.
‖ Reported administration times varied, but the IQCODE can be self-administered in less than 20 minutes, so was included.
†† Confidence intervals could not be calculated.
** Calculated using the sensitivity, specificity, and prevalence of MCI.
£ PPV and NPV reported in the text do not match what was calculated using the sensitivity, specificity, and prevalence of MCI. The numbers presented have been calculated.

Abbreviations: AUC = area under the curve; CAMCI = Computer Assessment of Mild Cognitive Impairment; CI = confidence interval; Est = estimated; HS = high school; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; MCI = Mild Cognitive Impairment; N = number; norm = normal; NPV = Negative Predictive Value;NR = not reported; PC = primary care; PPV = positive predictive value; SAGE = Self-administered Gerocognitive Examination; SD = standard deviation; SE = standard error; Sens = sensitivity; Spec = specificity; y = year.

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Table 7. Study Characteristics and Outcomes for Cognitive Impairment Screening (MCI/Dementia vs. Normal), Very Brief Instruments

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Borson, 2006[57] Fair	Mini-cog (primary language spoken)	3-4	371 371	Community	NR NR NR	40.2 12.1	CDR ≤0.5 All	2/3	84* (78.6, 88.5*)	87.9* (81.3, 92.8*)	91.9* (87.4, 95.2*)	76.9* (69.6, 83.2*)	NR
Holsinger, 2012[58]	Mini-cog	3-4	639 630	≥65 y PC	74.8 7.1 NR	3.3 39.2	Mayo criteria All	2/3	39 (34, 45)	78 (73, 82)	56.8** (49.3, 64.0**)	63.4** (58.7, 67.9**)	NR
Holsinger, 2012[58]	Memory Function 2 (MF-2)	1.5	639 630	≥65 y PC	74.8 7.1 NR	3.3 39.2	Mayo criteria All	Both yes	24 (19, 29)	93 (90, 95)	71.9** (61.4, 80.9**)	62.3** (58.1, 66.4**)	NR
Li, 2006[97] Fair	Informant Report of Memory Problems (IRMP) (Chinese or English)	1-2	144 NR	65-90 y Community; neuroscience clinic	72.7 50.7 4.7	13.2 25.7	Mayo criteria and CDR=0.5 All	NR	NR	NR	NR	NR	0.832 (0.037)
Callahan, 2002[67] Fair	6-item screener	1-2	2212 344	≥65 y Black Community	74.4 59.4 12.1	4.3 26.4	Mayo criteria Subset	≥2	74.2 (64.5, 83.3**)	80.2 (74.8, 85.0**)	57.4 (48.2, 66.7**)	89.6 (85.1, 93.4**)	0.86 (NR)
Galvin, 2005[103] Fair	AD8	<3	236 236	PC referral; Community	78.1 53 NR	24 29	CDR=0.5 All	≥2	85 (77, 91**)	86 (78, 92**)	86.8**£ (79.4, 92.3**)	84 (75.4, 89.8**)	90 (NR)
Holsinger, 2012[58]	Memory Impairment Screen (MIS)	4	639 630	≥65 y PC	74.8 7.1 NR	3.3 39.2	Mayo criteria All	2/3	17 (13, 22)	98 (96, 99)	86.8** (74.7, 94.5**)	61.5** (57.4, 65.5**)	NR

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Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Li, 2006[97] Fair	Brief IADL (4IADL) (Chinese or English)	<5‡ NR	144 NR	65-90 y Community; neuroscience clinic	72.7 50.7 4.7	13.2 25.7	Mayo criteria and CDR=0.5 All	NR	NR	NR	NR	NR	0.847 (0.033)
Cruz-Orduna, 2011[71] Fair	Functional Activities Questionnaire (FAQ) (Spanish)	5	160 160	Cognition-related complaint PC	72.4 70 88.8% ≤primary school	9.4 46.9	Below 10th percentile on at least one test All	1/2	73.33 (62.97, 82.11**)	72.86 (60.90, 82.80**)	77.65 (67.3, 86**)	68.00 (56.2, 78.3**)	0.77 (0.69, 0.84)

* Calculated from 2x2 table.
‡ Assumed.
‖ Reported administration times varied, but the IQCODE can be self-administered in less than 20 minutes, so was included.
†† Confidence intervals could not be calculated.
** Calculated using the sensitivity, specificity, and prevalence of cognitive impairment.
£ PPV reported in the text does not match what was calculated using the sensitivity, specificity, and prevalence of MCI. The number presented has been calculated.
Abbreviations: AD-8 = Alzheimer's Disease 8-item Questionnaire; AUC = area under the curve; CDR = clinical dementia rating; CI = confidence interval; Est = estimate ; FAQ = Functional Activities Questionnaire; IADL = instrumental activities of daily living; IRMP = Informant Report of Memory Problems; MCI = mild cognitive impairment; MF-2 = Memory Function 2; MIS = memory impairment screen; N = number; NPV = negative predictive value; NR = not reported; PC = primary care; PPV = positive predictive value; SE = standard error; SD = Standard Deviation; y = year.

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Table 8. Study Characteristics and Outcomes For Cognitive Impairment Screening (MCI/Dementia vs. Normal), Brief Instruments

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia % MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Vercambre, 2010[104] Fair	Telephone interview for Cognitive Impairment (TICS) (French)	7-9	120 120	Born between 1925 and 1930 Women National Education System	78.8 100 NR	8.3 (probable & possible) 15	Mayo criteria All	NR	NR	NR	NR	NR	0.78 (NR)
Manly, 2011[75] Fair	TICS-modified (TICS-M) (English or Spanish)	7-9	377 377	≥65 y PC	81.4 68.2 10.4	14.1 18.0	Mayo criteria All	≤26	73 (64, 80**)	77 (71, 82**)	59 (51.5, 67.9**)	86 (80.4, 89.9**)	0.81 (NR)
Vercambre, 2010[104] Fair	TICS-M (French)	7-9	120 120	Born between 1925 and 1930 Women National Education System	78.8 100 NR	8.3 (probable & possible) 15	Mayo criteria All	27 31 34	46 (28, 66**) 71 (51, 87**) 86 (67, 96**)	99 (94, 100**) 83 (73, 90**) 47 (36, 57**)	93 (66.1, 99.8**) 56 (38.1, 72.1**) 33 (22.3, 44.9**)	86 (77.7, 91.9**) 90 (82.1, 95.8**) 91 (79.6, 97.6**)	0.83 (NR)
Callahan, 2002[67] Fair	Mini-Mental State Examination (MMSE)	7-10	2212 269	≥65 y Black Community	74.4 59.4 12.1	4.3 26.4	Mayo criteria Subset	23/24 24/25	53.3 (43.1, 64.4**) 71.5 (61.0, 80.4**)	92.1 (88.1, 95.1**) 89.5 (87.4, 100.0**)	70.9 (58.8, 81.3**) 66.9 (56.7, 76.2**)	84.6 (79.9, 88.8**) 89.5** (85.0, 93.0**)	0.84 (NR)

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Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia % MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Cruz-Orduna, 2011[71] Fair	MMSE (Spanish)	7-10	160 160	Cognition-related complaint PC	72.4 70 % None/ Incomplete: 44.4 % Primary: 44.4 % Superior: 5.6	9.4 46.9	Below 10th percentile on at least one test All	23/24	76.67 (66.57, 84.94**)	70.0 (57.87, 80.38**)	76.67 (66.6, 84.9**)	70.00 (57.9, 80.4**)	0.82 (0.76, 0.88)
Cullen, 2005[76] Fair	MMSE	7-10	1142 1115	≥65 y PC	74.8 68 9.9	3.9 4.8	AGECAT, criteria NR All	23/24	72.2 (62.1, 80.8**)	89.4 (65.3, 98.6**)	39.3** (32.1, 46.9**)	97.1** (95.8, 98.1**)	NR
Jeong, 2004[79] Good	MMSE (Korean)	7-10	235 235	≥65 y Community	73.5 66.4 1 (median)	19.6 23.0	Subjective and objective cognitive impair-ment, details NR All	20/21	82 (73, 89)	79 71, 86)	74.6** (65.4, 82.4**)	85.6** (78.2, 91.2**)	0.89 (0.02)
Jorm, 1996[80] Fair	MMSE	7-10	144 NR	POW/veteran	72.9 0 NR	NR NR	Mild memory impair-ment criteria NR All	NR	NR	NR	NR	NR	0.70 (0.05)
Lam, 2008[83] Fair	MMSE (Chinese)	7-10	459 459	Community	71.2 54.5 4.8	9.6 35.3	Mayo criteria All	NR	NR	NR	NR	NR	0.961 (NR)

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Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia % MCI	Diagnostic Criteria / Verification	Cut Point	Sens (95% CI or SE)	Spec (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Li, 2006[97] Fair	MMSE (Chinese or English)	7-10	144 NR	65-90 y Community; neuroscience clinic	72.7 50.7 4.7	13.2 25.7	Mayo criteria and CDR=0.5 All	NR	NR	NR	NR	NR	0.779 (0.040)
McDowell, 1997[84] Fair	MMSE (English or French)	7-10	1600 1600	≥65 y Community	80.0 59 8.6	23 30	CIND criteria NR Subset	NR	NR	NR	NR	NR	0.77 (0.012)
Scharre, 2010[87] Fair	MMSE	7-10	254 63	>59 y Geriatric outpatient; community; independent and assisted living facilities; senior centers; memory clinic	78 66.7 93.7% ≥HS	33 33	≥1.5 SD below norm Subset	≤27	71 (55, 84**)	90 (70, 99**)	93.8** (79.2, 99.2**)	61.3** (42.2, 78.2**)	0.804 (NR)
Vercambre, 2010[104] Fair	MMSE (French)	7-10	120 120	Born between 1925 and 1930 Women National Education System	78.8 100 NR	8.3 15	Mayo criteria All	NR	NR	NR	NR	NR	0.72 (NR)
Markwick, 2012[89] Good	MoCA	10	107 107	MMSE ≥24 NR	76 54 76.6% >12 y	7.5 18.7	Petersen criteria All	<26	85.7* (67.3, 96.0*)	76.0* (65.0, 84.9*)	55.8* (39.9, 70.9*)	93.8* (84.8, 98.3*)	NR
Li, 2006[97] Fair	Immediate Recall (Logical Memory I) (Chinese or English)	<7‡	144 NR	65-90 y Community; neuroscience clinic	72.7 50.7 4.7	13.2 25.7	Mayo criteria and CDR=0.5 All	NR	NR	NR	NR	NR	0.871 (0.032)

* Calculated from 2x2 table.
‡ Assumed.
‖ Reported administration times varied, but the IQCODE can be self-administered in less than 20 minutes, so was included.
†† Confidence intervals could not be calculated.
** Calculated using the sensitivity, specificity, and prevalence of cognitive impairment.
Abbreviations: AGECAT = Automated Geriatric Examination for Computer Assisted Taxonomy; AUC = area under the curve; CDR = clinical dementia rating; CI = confidence interval; CIND = cognitive impairment no dementia; Est = estimate; HS = high school; MMSE = Mini-Mental State Examination; N = number; norm = normal ; NPV = negative predictive value ; NR = not reported; POW = prisoner of war; PPV = positive predictive value; SD = standard deviation; SE = standard error; TICS-M = Telephone interview for Cognitive Impairment modified; y = year.

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Table 9. Study Characteristics and Outcomes for Cognitive Impairment Screening (MCI/Dementia vs. Normal), Self-Administered Instruments

Study, Quality	Instrument (non-English Language)	Est. Time (Min)	N Screened, N Analyzed	Selection Criteria	Age (y), % Female, Education (y)	% Dementia % MCI	Diagnostic Criteria / Verification	Cut Point	Sens. (95% CI or SE)	Spec. (95% CI or SE)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI or SE)
Jorm, 1996[80] Fair	Short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)	NR‖	144 NR	POW/veteran	72.9 0 NR	NR NR	Mild memory impairment criteria NR All	NR	NR	NR	NR	NR	0.74 (0.05)
Jorm, 1996[80] Fair	Full IQCODE	NR‖	144 NR	POW/veteran	72.9 0 NR	NR NR	Mild memory impairment criteria NR All	NR	NR	NR	NR	NR	0.75 (0.05)
Cruz-Orduna, 2011[71] Fair	Full IQCODE (Spanish)	NR‖	160 160	Cognition-related complaint PC	72.4 70 88.8% ≤primary school	9.4 46.9	Below 10th percentile on at least one test All	3.31/ 3.35	71.11 (60.60, 80.18**)	74.29 (62.44, 83.99**)	78.05 (67.5, 86.4**)	66.67 (55.1, 76.9**)	0.75 (0.67, 0.82)
Tokuhara, 2006[90] Fair	Full IQCODE	NR‖	299 230	≥65 y Japanese/ Okinawan PC	74.2 66 12.2	7 10	Criteria NR All	3.3	82.6 (NR††)	83.0 (NR††)	NR††	NR††	0.87 (NR)
Scharre, 2010[87] Fair	Self-administered Gerocognitive Examination (SAGE)	10-15	254 63	>59 y Geriatric outpatient; community; independent and assisted living facilities; senior centers; memory clinic	78 66.7 93.7% ≥HS	33 33	≥1.5 SD below norm Subset	≤16	79 (63, 90)	95 (76, 100)	97.1** (84.7, 99.9**)	69.0** (49.2, 84.7**)	0.919 (NR)

* Calculated from 2x2 table.
‡ Assumed.
‖ Reported administration times varied, but the IQCODE can be self-administered in less than 20 minutes, so was included.
†† Confidence intervals could not be calculated.
** Calculated using the sensitivity, specificity, and prevalence of cognitive impairment.

Abbreviations: AUC = area under the curve; Est = estimate; HS = high school; IQCODE = Short Informant Questionnaire on Cognitive Decline in Elderly; MCI = mild cognitive impairment; Min = minute; MMSE = Mini-Mental State Examination; N = number; NR = not reported; NPV = negative predictive; PC = primary care; POW = prisoner of war; PPV = positive predictive value; SAGE = Self-Administered Gerocognitive Examination; SD = standard deviation; SE = standard error; Sens = sensitivity; Spec = specitivity; Y = year.

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Table 1. Baseline Population Characteristics for AChEI Trials

Medication	Author, year USPSTF Quality Rating	N randomized	Mean Age (y)	% Female	% Non-White	% Institutionalized, Assisted Living	Mean MMSE (MMSE inclusion criteria)	%MCI % Dementia	Specific condition	Mean Education (y)
Donepezil	Doody, 2009[105,106] Fair	IG: 409 CG: 412	70	46	13	NR	27.5 (24-28)	MCI: 100 Dementia: 0	MCI	0-7: 0.6% 8-15: 52.8% >15: 46.5%
	Mori, 2012[107] Fair	IG1: 35 IG2: 33 IG3: 37 CG: 34	79	66	100	NR	19.6 (10-26)	MCI: 0 Dementia: 100	DLB	NR
	Requena, 2004[108,109] Fair	IG: 30 CG: 18	77	71	NR	NR	20.8 (NR)	MCI: 0 Dementia: 100	AD	NR
Galantamine	Auchus, 2007[110] GAL-INT-26 Study Fair	IG: 397 CG: 391	72	36	8	NR	20.3 (10-26)	MCI: NR Dementia: 100	VaD	NR
	Rockwood, 2006[111-114] VISTA Fair	IG: 64 CG: 66	77	63	NR	0	20.3 (10-25)	MCI: 0 Dementia: 100	AD (probable)	11.0
Rivastigmine	Ballard, 2008[115] VantagE Study Fair	IG: 365 CG: 345	73	38	18	NR	19.2 (10-24)	MCI: 0 Dementia: 100	VaD (including probable)	9.3
	Feldman, 2007[116] Study 304 Fair	IG1: 227 IG2: 229 CG: 222	71	59	NR	0	18.6 (10-26)	MCI: NR Dementia: 100	AD	NR
	Mok, 2007[117] Fair	IG: 20 CG: 20	75	60	100	NR	13.2 (3-24)	MCI: NR Dementia: 100	VaD (subcortical)	3.3
	Winblad, 2007[118-127] IDEAL Study Fair	IG1: 293 IG2: 303 IG3: 297 CG: 302	74	67	25	3	16.5 (10-20)	MCI: 0 Dementia: 100	AD (including probable)	9.9

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Medication	Author, year USPSTF Quality Rating	N randomized	Mean Age (y)	% Female	% Non-White	% Institutionalized, Assisted Living	Mean MMSE (MMSE inclusion criteria)	%MCI % Dementia	Specific condition	Mean Education (y)
Memantine	Bakchine, 2008[128] Good	IG: 318 CG: 152	74	63	0	NR	18.7 (11-23)	MCI: 0 Dementia: 100	AD (probable)	NR
	Ferris, 2007[129] Fair	IG: 30 CG: 30	67	65	10	NR	28.8 (>26)	MCI: 100 Dementia: 0	MCI	NR
	Porsteinsson, 2008[130] MEM-MD-12 Study Good	IG: 217 CG: 216	75	52	NR	0	16.8 (10-22)	MCI: 0 Dementia: 100	AD (probable)	NR
	Saxton, 2012[131] MEM-MD-71 Good	IG: 136 CG: 129	75	58	9	0	15.8 (10-19)	MCI: 0 Dementia: 100	AD (probable)	11.5
	Wilkinson, 2012[132] Fair	IG: 134 CG: 144	74	57	<1	0	16.9 (12-20)	MCI: 0 Dementia: 100	AD (probable)	NR

Abbreviations: AChEI = acetylcholinesterase inhibitor; AD = Alzheimer's disease; CG = control group; DLB = dementia with Lewy bodies; IDEAL = Investigation of transDermal Exelon in Alzheimer's disease; IG = intervention group; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; Multi = multi-country; N = number; NR = not reported; US = United States; VaD = vascular dementia; y = year.

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Table 2. Study Characteristics for AChEI Trials

Medication	Author, year USPSTF quality rating	Daily dosage	N randomized	Location	Longest f/u (m)	% followed up	Funding source	Inclusion criteria	Exclusion criteria	Diagnostic criteria
Donepezil	Doody, 2009[105,106] Fair	5-10 mg	IG: 409 CG: 412	US	11	61	Eisai; Pfizer	Healthy, ambulatory or ambulatory-aided amenstic subjects with MCI; 45 to 90 y old; expressed a memory complaint representing a change from previous functioning (corroborated by an informant and confirmed by neuropsychological testing scores); had an informant with daily contact; CT scan or MRI within 12 months of screening showing no clinical evidence of infection, infarction, other focal lesions or clinically significant comorbid pathologies.	Diagnosis of probably or possible VaD (NINCDS-ADRDA, DSM-IV criteria) or another form of dementia; a neurologic or psychiatric disorder, a sleep disorder that could affect cognitive performance; drug or alcohol abuse or dependence within the previous 5 y; uncontrolled hypertension regardless of antihypertensive medication; uncontrolled diabetes mellitus; any other medical condition deemed incompatible with participation; past treatment with AChEI or memantine for >1 month or within previous 3 months; taking concomitant anticholinergics, anticonvulsants, antiparkinson agents, stimulants, cholingeric agents, antipsychotics, antidepressants or anxiolytics with anticholinergic or procholinergic effects.	Memory component corroborated by informant and confirmed by neuropsychological scores (CDR 0.5 with Memory Box score 0.5 or 1.0, no box score >1.0; MMSE score 24-28; Logical Memory II Delayed Paragraph Recall subtest of Weschsler Memory Scale-Revised score ≤8 (16+ y education), ≤4 (8-15 y education), or ≤2 (<8 y education); Rosen modified Hachinski Ischemia scale score ≤4

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Medication	Author, year USPSTF quality rating	Daily dosage	N randomized	Location	Longest f/u (m)	% followed up	Funding source	Inclusion criteria	Exclusion criteria	Diagnostic criteria
	Mori, 2012[107] Fair	3-10 mg	IG1: 35 IG2: 33 IG3: 37 CG: 34	Japan	3	87.9	Eisai	Outpatients who met probable DLB criteria (McKeith) aged 50 y or older with mild to moderate-severe dementia (MMSE 10-26; CDR ≥ 5) with behavioral symptoms (NPI+ ≥ 8); caregivers who routinely stayed with them at least 3 days a week and 4 hours per day provided informaiton to study, assisted in compliance and escorted patients to required visits	Parkinson disease diagnosed at least 1 year prior to onset of dementia; focal vascular lesions on MRI or CT that might cause cognitive impairment or other neurological or psychiatric diseases; clinically significant systemic disease; complications of history of sever GI ulcer, severe asthma, or obstructive pulmonary disease; systolic hypotension (<90 mm Hg); bradycardia (<50/m); sick sinus syndrome; atrial or atrioventricular conduction block; QT interval prolongation (450+ msec); hypersensitivity to donepezil or piperidine derivatives; severe parkinsonism (Hoehn and Yahr score IV+); treatment with ChEI or any investigational drug within 3 months prior to screening	McKeith
	Requena, 2004[108,109]	5-10 mg	IG: 30 CG: 18	Spain	24	96.5	Pfizer	DSM-IIIR and NINCDS-ADRDA for AD	Severe dementia; loss of all capacity of speech; requiring assistance for all daily activities; loss of basic psychomotor abilities; lack of capacity	DSM-IIIR; NINDS-ADRDA

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Medication	Author, year USPSTF quality rating	Daily dosage	N randomized	Location	Longest f/u (m)	% followed up	Funding source	Inclusion criteria	Exclusion criteria	Diagnostic criteria
									to express emotions adequately; apparent failure of the brain to give orders to the body; appearance of generalized and cortical neurological signs and symptoms.	
Galantamine	Auchus, 2007[110] GAL-INT-26 Study Fair	16-24 mg	IG: 397 CG: 391	Multi	6	80.5	NR	NINDS-AIREN diagnosis of VaD with MRI confirmation of clinical diagnosis; MMSE score 10-26; ADAS-cog score ≥12; onset of disease at age 40-90 y; availability of caregiver.	Diagnosis of AD, Parkinson's disease, Hungington disase, other neurodegenerative dementia; serious coexisting medical condition; CVD that would limit trial participation; or already taking drugs to treat dementia.	NINDS-AIREN
	Rockwood, 2006[111-114] VISTA Fair	16-24 mg	IG: 64 CG: 66	Canada	4	84	Janssen-Ortho Canada; Canadian Institute of Health Research	English-speaking individuals with probable AD (NINCDS-ADRDA); mild-to-moderate dementia (MMSE score 10-25; ADAS-cog score ≥18); had daily contact with a responsible caregiver.	Resided in nursing homes; disabling communication difficulties (problems in language, speech, vision or hearing); other active medical issues or competing causes of dementia; took anti-dementia medications within 30 days before screening; hypersensitive to cholinomimetic agents or bromide; participated in other galantamine trials.	NINDS-ADRDA

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Medication	Author, year USPSTF quality rating	Daily dosage	N randomized	Location	Longest f/u (m)	% followed up	Funding source	Inclusion criteria	Exclusion criteria	Diagnostic criteria
Rivastigmine	Ballard, 2008[115] VantagE Study Fair	3-12 mg	IG: 365 CG: 345	Multi	6	80.6	Novartis	Men or women aged 50-85 y with a diagnosis of VaD according to DSM-IV and a diagnosis of probable VaD according to NINDS-AIREN criteria; MMSE 10-24; contact with a responsible caregiver on at least 3 days per week; written informed consent.	Any primary neuro-degenerative disorder other than VaD or any other causes of dementia; a major depressive episode; active, uncontrolled seizure disorder; any disability or unstable disease that may prevent the patient from completing all study requirements; current diagnosis of bradycardia (hr <50 bpm), sick sinus syndrome, or conduction effects; unstable or poorly controlled blood pressure over the past 3 months; current diagnosis of uncontrolled atrial fibrillation (hr>100 bpm); presence of any metal objects (e.g. pacemaker) within the patient that prevented him or her from undergoing an MRI scan.	DSM-IV; NINDS-AIREN
	Feldman, 2007[116] Study 304 Fair	2-12 mg	IG1: 227 IG2: 229 CG: 222	Multi	6	82	Novartis	Community dwelling patients at least 50 y old and met criteria for Alzheimer's disease (DSM-IV) and in accordance with criteria for probable AD of the NINDS-ADRDA); MMSE score 10-26.	Severe and unstable cardiac disease, severe obstructive pulmonary disease or other life threatening conditions.	DSM-IV; NINDS-ADRDA

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Medication	Author, year USPSTF quality rating	Daily dosage	N randomized	Location	Longest f/u (m)	% followed up	Funding source	Inclusion criteria	Exclusion criteria	Diagnostic criteria
	Mok, 2007[117] Fair	6 mg	IG: 20 CG: 20	China	6	98	Norvartis	Chinese patients with subcortical VaD, aged 40-90 y and MMSE score 3-24.	Other concurrent dementing diseases (e.g., B12 deficiency), unstable medical conditions, stroke within 3 months of study, concurrent use of cholinergic drugs, frequent changes in dose of centrally acting drugs (e.g., benzodiazepines) 3 months prior to study entry, severe dementia or language problems making participant in cognitive testing impossible, and no close caregivers (defined by <3 visits/week).	Standardized criteria to define subcortical vascular dementia and brain imaging criteria, both by Erkinjuntti
	Winblad, 2007[118-127] IDEAL Study Fair	9.5-17.4 mg/24 hours patch; 12 mg capsule	IG1: 293 IG2: 303 IG3: 297 CG: 302	Multi	6	81.2	Norvartis	Women or men aged 50-85 y with a diagnosis of dementia of the Alzheimer's type (DSM-IV) and probable AD (NINDS-ADRDA); brain scan within one year prior to randomization; MMSE score 10-20; living with someone in the community or if living alone, in daily contact with a responsible caregiver.	Advanced, severe, progressive, or unstable disease of any type that would interfere with study assessment or put the patient at special risk; any condition other than AD that could explain dementia; use of any investigational drugs, new psychotropic or dopaminergic agents, cholinesterase inhibitors or anti-cholinergic agents in previous 4 weeks.	DSM-IV; NINDS-ADRDA

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Medication	Author, year USPSTF quality rating	Daily dosage	N randomized	Location	Longest f/u (m)	% followed up	Funding source	Inclusion criteria	Exclusion criteria	Diagnostic criteria
Memantine	Bakchine, 2008[128] Good	20 mg	IG: 318 CG: 152	Multi	6	87	H. Lundbeck A/S	Probable Alzheimer's Disease (see dementia diagnosis) with a CT or MRI of the brain within the past 12 months with results consistent with such diagnosis; outpatient; >50 y old; MMSE score 11-23; reliable and knowledgeable caregiver who could accompany subject to all visits during the study.	VaD, dementia or clinically significant neurological disease other than AD, major depressive disorder or a modified Haskinski Ischemic Rating Scale scale >4; clinically significant coexisting medical conditions or lab abnormalities; receiving anticonvulsants, antiparkinson agents, classical and depot antipsychotics, anxiolytics, hypnotics, non-SSRI antidepresants, cholinesterase inhibitors, or any other investigational products.	DSM-IV; NINDS-ADRDA
	Ferris, 2007[129] Fair	20 mg	IG: 30 CG: 30	US	3	90	Forest Research Institute	Men and women aged 50 to 79 y who complained that they have experienced memory loss over the course of adult life and performed at least one standard deviation below the mean for young adults on a standardized memory test.	MMSE score ≤26; showed other evidence of dementia; depression (GDS score of ≥ 11); showed evidence on history or examination or medical or neurologic problems that could account for memory loss over the course of decades; taking or were likely to require over the course of the study a wide range of drugs that can impair cognition.	Reported memory loss over the course of their adult life and performed at least one standard deviation below the mean for young adults on a standardized memory test

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Medication	Author, year USPSTF quality rating	Daily dosage	N randomized	Location	Longest f/u (m)	% followed up	Funding source	Inclusion criteria	Exclusion criteria	Diagnostic criteria
	Porsteinsson, 2008[130] MEM-MD-12 Study Good	20 mg	IG: 217 CG: 216	US	6	89	Forest Labs	Subjects with probable AD using NINCDS-ADRDA criteria; MMSE score 10-22; minimum age 50 y; CT or MRI within 12 months consistent with probably AD diagnosis; treatment with a cholinesterase inhibitor for 6 months or longer; stable dose regimine for 3 months or longer (donepezil 5 or 10 mg/day; rivastigmine 6, 9, 12 mg/day; galantamine 16 or 24 mg/day); knowledgeable and reliable caregiver to accompany and supervise participant; MADRS score <22; ability to ambulate; vision and hearing capabilities to permit compliance with assessments; and medically stable condition. At least 2 y post-menopausal or surgically sterile (females only).	Clinically significant and active pulmonary, GI, renal, hepatic, endocrine or CVD; vitamin B12 or folate deficiency; evidence of any psychiatric or neurologic disorder; dementia complicated by organic disease or AD with delusions or delirium; Hachinski Ischemi Score >4; oncology diagnosis and ongoing/recent (within 6 months); poorly controlled hypertension; substance abuse; depot neuroleptic use within 6 months; positive urine drug test; likely institutionalization during trial; previous memantine treatment; participation in an investigational drug treatment (including memantine) within last 30 days; and likely cessation of cholinesterase treatment during trial.	NINDS-ADRDA
	Saxton, 2012[131] MEM-MD-71 Good	20 MG	IG: 136 CG: 129	Multi	3	94.7	Forest Labs	Native English speakers with NINCDS-ADRDA diagnosis of probable AD, MMSE 10-19, CT or MRI results within the past 12 months consistent with diagnosis,	Clinically significant and active pulmonary, GI, renal, hepatic, endocrine, or CVD or cancer; evidence of psychiatric or neurologic disorders other than probable AD;	NINCDS-ADRDA

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Medication	Author, year USPSTF quality rating	Daily dosage	N randomized	Location	Longest f/u (m)	% followed up	Funding source	Inclusion criteria	Exclusion criteria	Diagnostic criteria
								stable dose ofChEI (if taking) for at least 3 months, pass physical exam, laboratory evaluation and ECG; ambulatroy or ambulatory-aided with vision and hearing capabilities sufficient for completion of the study; females must be surgically sterile or postmenopausal for at least 2 y; knowledgable and reliable caregive who spoke English and would accompany subject at visit	dementia complicated by other organic brain disease or predominant delusions; clinically significant vitamin B12 or folate defienciency; Hachinski Ischemic Score >4; hypertension (SBP >180 mm Hg; DBP >100 mm Hg); hypotension (SBP <90 mm Hg; DBP <50 mm Hg); history of alcoholism and drug abuse within the past 5 y; severe renal impairment or impaired kidney function, preivous memantine treatment, participation in memantine trial, hypersensitivity to amantadine or rimantidine, likely institutionalized during trial; any other condition that make patient or caregiver unsuitable for trial	
	Wilkinson, 2012[132] Fair		IG: 134 CG: 144	Multi	12	78.1	H. Lundbeck A/S; Merz Pharma-ceuticals GmbH	Outpatients aged ≥50 y with a diagnosis of probable AD (NINCDS-ADRDA) consistent with MRI scan; MMSE 12-20, healthy, ambulatory or ambulatory aided, relibale caregiver, fluent speaker of native language, women had to	Clinically significant and active pulmonary, GI, renal, hepatic, endocrine, or CVD; severe renal impairment, high or low BP, hypersensitivity to memantine, amantadine, rimantidine, or lactose; any clinically significant	NINCDS-ADRDA

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Medication	Author, year USPSTF quality rating	Daily dosage	N randomized	Location	Longest f/u (m)	% followed up	Funding source	Inclusion criteria	Exclusion criteria	Diagnostic criteria
								be at least 2 y post-menopausal or surgically sterile, with or without stable current AChEI treatment allowed	neurodegenerative disease or other serious neurological diosrder other than AD; unable to tolerate MRI, further scans scheduled during study or contraindicated for MRI; modified Hachinski Ischemia score >4, foreseen to enter a nursing or residential home within the next 12 months; VaD (NINDS-AIREN) criteria from MRI scan	

Abbreviations: AChEI = acetyl cholinesterase inhibitor; AD = Alzheimer's disease; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; bpm = beats per minute; CDR = Clinical Dementia Rating; CG = control group; CT = computed tomography; CVD = cardiovascular disease; DBP = diastolic blood pressure; DLB = dementia with Lewy bodies; DSM = Diagnostic and Statistical Manual; ECG = electrocardiogram; f/u = followup; GDS = Geriatric Depression Scale; GI = gastrointestinal; hr = heart rate; IG = intervention group; MADRS = Montgomery-Asberg Depression Rating Scale; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; m = months; MRI = magnetic resonance imaging; Multi = multi-country; N = number; NINDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN = National Institute of Neurological Disorders and Stroke and the Association Internationale pour las Recherche et l'Enseignment en Neurosciences; NPI = neuropsychiatric inventory; NR = not reported; RCT = randomized controlled trial; SBP = systolic blood pressure; SSRI = selective serotonin reuptake inhibitor; USPSTF = U.S. Preventive Services Task Force; VaD = vascular dementia.

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Table 3. Study Characteristics for Other Medication and Supplement Trials

Medication Group	Study reference USPSTF quality rating	Medication Dose	Funding Source	n rand	Location	MCI or Dementia (Type) MMSE Score (mean)	Mean Age	% Female	Mean Edu (y)	% Assist Living	Diagnostic Criteria
Vascular medications	AD2000[133] Fair	ASA, 75mg	Gov	IG: 156 CG: 154	UK	Dementia (AD**) 19.0	75†	63	NR	0	DSM-IV
	Feldman, 2010[134] Jones, 2008[135] LEADe study Fair	Atorvastatin, 80 mg	Ind	IG: 314 CG: 326	US	Dementia (AD) 21.9	74	52	NR	"A few in assisted living"	NINCDS-ADRDA; DSM-IV
	Sano, 2011[136] Fair	Simvastatin, 40 mg	Ind; Gov	IG: 204 CG: 202	US	Dementia (AD) 20.4	75	59	14.3	NR	NINCDS-ADRDA
	Simons, 2002[137] Fair	Simvastatin, 80 mg	Ind; Gov	IG: 24 CG: 20	Germany	Dementia (AD) 17.5	68	55	NR	NR	NINCDS-ADRDA
	Sparks, 2005[138] Sparks, 2006[139] Sparks, 2006[140] ADCLT trial Fair	Atorvastatin, 80 mg	Pri; Ind	IG: 32 CG: 31	US	Dementia (AD) 20.8	79	37	13.7	NR	NINCDS-ADRDA
	Clarke, 2003[141] Fair	Aspirin, 81 mg	Gov; Ind*; Pri	IG: 74 CG: 75	UK	Mixed (NR) 21†	75†	NR	NR	0	DSM-IV (dementia); symptoms of memory problems (MCI)
NSAIDS	Pasqualetti, 2009[142] Fair	Ibuprofen, 800 mg	Gov; Ind*	IG: 66 CG: 66	Italy	Dementia (AD) 20.0	74	63	7.2	NR	NINCDS-ADRDA
	Aisen, 2003[143]	Naproxen, 220 mg	Gov; Ind*	IG: 118 CG: 111	US	Dementia (AD)	74	53	14.0	NR	NINCDS-ADRDA

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Medication Group	Study reference USPSTF quality rating	Medication Dose	Funding Source	n rand	Location	MCI or Dementia (Type) MMSE Score (mean)	Mean Age	% Female	Mean Edu (y)	% Assist Living	Diagnostic Criteria
	Fair					20.9					
	de Jong, 2008[144] Fair	Indomethacin, 100 mg	Pri	IG: 26 CG: 25	Netherlands	Dementia (AD) 19.6	73	65	2.5‡	NR	NINCDS-ADRDA
	Soininen, 2007[145] Fair	Celecoxib, 40 mg	Ind	IG: 23 CG: 13	Multi	Dementia (AD) 19.7	74	55	NR	NR	NINCDS; DSM-IV
Gonadal Steroids	Henderson, 2000[146] Fair	Estrogen, 1.25 mg	Ind*	IG: 21 CG: 21	US	Dementia (AD) 19.5	78	100	% HS grad: 76	NR	NINCDS-ADRDA
	Lu, 2006[147] Fair	Testosterone, 75 mg	Gov; Pri	IG: 9 CG: 9	US	Dementia (AD) 22.0	70	0	16.6	NR	NINCDS-ADRDA
	Mulnard, 2000[148] Fair	Estrogen, 0.625mg and 1.25 mg	Gov; Ind*	IG: 39 CG: 39	US	Dementia (AD) 20.7	75	100	12.2	NR	NINCDS-ADRDA
	Valen-Sendstad, 2010[149] Fair	Progesterone, 0.5 mg + Estrogen, 1 mg	Ind; Pri	IG: 33 CG: 32	Norway	Dementia (AD) 21.9	81	100	%>9 y: 51	NR	DSM-IV or ICD-10
	Wang, 2000[150] Fair	Estrogen, 1.25 mg	Gov; Ind*	IG: 25 CG: 25	Taiwan	Dementia (AD) 16.2	72	100	5.9	NR	NINCDS-ADRDA
Vitamins and supplements	Aisen, 2008[151] Good	Folic acid, 5 mg + Vitamin B12, 1 mg + Vitamin B6, 25 mg	Ind*; Gov	IG: 240 CG: 169	US	Dementia (AD) 21.0	76	56	13.9	NR	NINCDS-ADRDA
	Clarke, 2003[141] Fair	Folic acid, 2 mg + Vitamin B12, 1 mg	Gov; Ind*; Pri	IG: 74 CG: 75	UK	Mixed (NR) 21†	75†	NR	NR	0	DSM-IV (dementia); symptoms of memory problems

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Medication Group	Study reference USPSTF quality rating	Medication Dose	Funding Source	n rand	Location	MCI or Dementia (Type) MMSE Score (mean)	Mean Age	% Female	Mean Edu (y)	% Assist Living	Diagnostic Criteria
											(MCI)
	Clarke, 2003[141] Fair	Vitamin E, 500 mg + Vitamin C, 200 mg	Gov; Ind*; Pri	IG: 75 CG: 74	UK	Mixed (NR) 21†	75†	NR	NR	0	DSM-IV (dementia); symptoms of memory problems (MCI)
	Connelly, 2008[152] Fair	Folic acid, 1 mg	Gov	IG: 30 CG: 27	UK	Dementia (AD) 23.5	76	71	NR	NR	NINCDS-ADRDA
	de Jager, 2012[153] VITACOG Fair	Folic acid 0.8 mg + Cyano-cobalamin 0.5 mg + Pyridoxine HCl 20 mg	Pri	IG: 138 CG: 133	UK	MCI NR	77	64	14.5	NR	Petersen's criteria
	Freund-Levi, 2006[154] Freund-Levi, 2008[155] Fair	DHA, 430 mg + EPA, 150 mg + Vitamin E, 4 mg	Pri; Ind	IG: 103 CG: 101	Sweden	Dementia (AD) 23.4	74	54	NR	0	DSM-IV
	Kwok, 2011[156] Fair	Methylcobalamin, 1 mg + Folic acid, 5 mg	Gov	IG: 70 CG: 70	Hong Kong	Dementia (AD and/or VaD) 16.6	78	64	%<3 y edu	NR	NINCDS-ADRDA
	Sano, 1997[157] Good	Vitamin E, 1000 IU	Gov; Ind*	IG: 85 CG: 84	US	Dementia (AD) 12.3	73	66	12.4	100	NR
	Sinn, 2012[158] Fair	1.55 g DHA + 0.4 g EPA 1.67 g EPA + 0.16 g DHA	Gov; Ind	IG1: 18 IG2: 18 CG: 18	Australia	MCI 27.2	74.1	32	NR	NR	International Working Group on MCI
	Quinn, 2010[159] Fair	DHA, 2 g	Gov; Ind	IG: 238 CG: 164	US	Dementia (AD)	76	52	14.0	NR	NR

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Medication Group	Study reference USPSTF quality rating	Medication Dose	Funding Source	n rand	Location	MCI or Dementia (Type) MMSE Score (mean)	Mean Age	% Female	Mean Edu (y)	% Assist Living	Diagnostic Criteria
						20.7					
	Sun, 2007[160] Fair	Mecobalamin, 0.5 mg + Multivitamin†	Gov; Ind*; Pri	IG: 45 CG: 44	Japan	Dementia (AD) 18.7	75	49	NR	NR	DSM-IV
	van Uffelen, 2008[161] van Uffelen, 2007[162] van Uffelen, 2005[163] Fair	Folic acid, 5 mg + Vitamin B12, 0.4 mg + Vitamin B6, 50 mg	Gov; Pri	IG: 90 CG: 89	Netherlands	Dementia (NR) 29.0	75	44	% low edu: 56	0	SMC
	Yurko-Mauro, 2010[164] Good	DHA, 900 mg	Ind	IG: 242 CG: 243	US	Dementia (NR) 28.2	70	58	14.6	NR	SMC and objectively identified decline in cognitive functioning (DSM-IV)

* Study drug only provided by industry; no other funding was provided.
** With or without VaD.
† Median.
‡ Mean education level (1=primary school, 5=university level).

Abbreviations: AD = Alzheimer's dementia; ASA = Acetylsalicylic Acid; CG = control group; DHA = docosahexaenoic acid; DSM-IV = Diagnostic and Statistical Manual IV; EPA = eicosapentaenoic acid; Edu = education; Gov = government; HCl = Hydrogen chloride; Ind = industry; IG-intervention group; IU- international unit; LEADe- Lipitor's Effect in Alzheimer's Dementia; MCI = mild cognitive impairment; mg = milligram; MMSE = mini mental state examination; N = number; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NR = not reported; Pri = private; Rand = randomized; SMC = subjective memory complaints; US = United States; UK = United Kingdom; VaD = vascular dementia.

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Table 4. Population Characteristics of Caregiver Intervention Trials

Group	Study reference USPSTF quality rating	Intervention Description	n rand	Location	CG Age, Mean (range)	CG % Female	CG Race/ Ethnicity	% Spouse	Patient MMSE Score (mean)	Amount of caregiving*
Group-based psychoeducation	Belle, 2006[165] REACH II Fair	Comprehensive, multicomponent psychoeducational program, including support group and computer-supported phone system	IG: 109 CG: 73	US	61 (NR)	83	NR	43	12.9	Minimum 4 hours/day
	Brodaty, 1989[166] Fair	10-day residential education, training, and support program for caregivers and patients, 10-day memory training program for patients	IG: 36 CG1: 32 CG2: 33	Australia	68 (NR)	54	NR	93	NR (Mean CDR: 1.1)	NR
	REACH-Birmingham[167] Fair	Psychoeducational and skills training program	IG: 70 CG: 70	US	63 (28–88)	79	59% White 41% Black	50	13.1	Minimum 4 hours/day
	Chu, 2011[168] Fair	Group education program	IG: 37 CG: 38	Taiwan	NR (NR)	57	NR	32	NR	Minimum 4 hours/day
	Coon, 2003[169] Fair	Psychoeducational and skill training with anger management (IG1)	IG1:53 IG2:64 CG:52	US	64 (NR)	100	NR	57	14.2	NR
	de Routrou, 2011[170] Fair	Comprehensive group psychoeducation	IG: 79 CG: 78	France	65 (NR)	68	NR	57	NR	Minimum 4 hours/week
	REACH Palo Alto[171] Fair	Coping with Caregiving class.	IG:99 CG:43	US	57 (23–90)	100	57% White 48% Hispanic	NR	13.7	Minimum 4 hours/day
	Gallagher-Thompson, 2008[172]	Cognitive-behavior program on coping with	IG: 87 CG: 97	US	58 (NR)	100	52% White 48%	38	14	Minimum 8 hours/week

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Group	Study reference USPSTF quality rating	Intervention Description	n rand	Location	CG Age, Mean (range)	CG % Female	CG Race/ Ethnicity	% Spouse	Patient MMSE Score (mean)	Amount of caregiving*
	Fair	caregiving					Hispanic			
	Hebert, 1994[173] Fair	Group psychoeducational program	IG: 24 CG: 21	Canada	61 (30–90)	63	NR	68	14.6	Minimum 1 day/week
	Hepburn, 2001[174] Fair	Minnesota Family Workshop	IG:72 CG:45	US	65 (NR)	70	100% White	66	NR	NR
	Hepburn, 2005[175] Fair	Partners in Caregiving (PIC) program, focus on day-to-day caregiving (IG1) or decision-making framework IG2), but groups combined for results	IG:151 CG:64	US	66 (NR)	76	NR	66	18.6	NR
	Kurz, 2010[176] Fair	Group education program	IG:156 CG:136	Austria, Switzerland, Germany	62 (NR)	69	NR	58	13.9	Minimum daily contact
	Losada, 2010[177] Fair	Group caregiver training	IG: 88 CG: 79	Spain	60 (33-84)	83	NR	35	NR	Minimum 1 hour/day
	Ostwald, 1999[178] Fair	Multifaceted curriculum delivered via lectures and video	IG:72 CG:45	US	66 (NR)	65	NR ("almost all" White)	NR	NR	NR
	Ulstein, 2007[179] Fair	Group education program	IG:90 CG:90	Norway	65 (NR)	64	NR	70	20.8	Minimum weekly contact
	Waldorff, 2012[180] Good	Group courses targeting caregiver and patient plus individual sessions for dyad	IG: 163 CG: 167	Denmark	66 (NR)	67	NR	65	24.1	Weekly

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Group	Study reference USPSTF quality rating	Intervention Description	n rand	Location	CG Age, Mean (range)	CG % Female	CG Race/ Ethnicity	% Spouse	Patient MMSE Score (mean)	Amount of caregiving*
Individual psychoeducation	Chang, 1999[181] Fair	Video-based information and phone counseling	IG:46 CG:41	US	67 (NR)	NR	NR	89	NR	NR
	Ducharme, 2011[182] Fair	Individualized counseling and education program	IG:64 CG:57	Canada	61 (NR)	79	NR	34	NR	NR
	Gitlin 2008[183] Fair	Tailored activity program: identify and capitalize on preserved patient abilities	IG:30 CG:30	US	65 (47–90)	88	77% White 22% Black 1% Other	62	11.6	Minimum 4 hours/day
	Gitlin 2001[184] Fair	Targeted multi-component program by occupational therapists	IG:100 CG:102	US	61 (23–92)	73	74% White 26% Non-White	25	NR	NR
	REACH Philadelphia[185,186] Fair	Environmental skill-building program	IG:89 CG:101	US	61 (28–95)	75	48% White 48% Black 2% Hispanic 2% Other	35	12.2	Minimum 4 hours/day
	Gitlin, 2010[187] ACT Fair	Occupational therapy intervention	IG:137 CG:135	US	66 (33–93)	82	70% White 30% Non-White	51	13	NR
	Gitlin, 2010[188] COPE Fair	Occupational Therapist assessment, education, and training	IG:117 CG:120	US	62 (NR)	89	70% White 28% Black 2% Other	38	13.4	Minimum 8 hours/week
	Graff 2006[189] Fair	Occupational therapy intervention	IG:68 CG:67	Netherlands	64 (NR)	70	NR	59	19.0	Minimum once/week
	Hebert 2003[190] Fair	Cognitive appraisal and coping strategies group psychoeducational program	IG:24 CG:21	Canada	60 (NR)	60	NR	61	NR	NR

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Group	Study reference USPSTF quality rating	Intervention Description	n rand	Location	CG Age, Mean (range)	CG % Female	CG Race/ Ethnicity	% Spouse	Patient MMSE Score (mean)	Amount of caregiving*
	Hinchliffe 1995[191] Fair	Individualized care package	IG:22 CG:18	UK	68 (37–89)	73	NR	70	NR	NR
	Huang 2003[192] Fair	Individualized counseling and education program	IG:30 CG:29	Taiwan	56 (28–80)	73	NR	35	13.1	NR
	Marriott 2000[193] Fair	Individualized counseling and education program	IG:14 CG1:14 CG2:14	UK	64 (NR)	69	NR	52	12.5	NR
	Martin-Carrasco 2009[194] Fair	Psychoeducation Intervention Program (PIP)	IG:55 CG:60	Spain	58 (NR)	69	NR	55	18.7	Minimum 4 hours/day
	Martin-Cook 2005[195] Fair	Individualized training program to help caregivers accurately assess patients' functioning and demonstrate simplifying tasks	IG:24 CG:25	US	NR (NR)	70	NR	92	19.4	NR
	Roberts 1999[196] Fair	Problem-solving counseling	IG:38 CG:39	Canada	62 (38–87)	70	NR	52	NR	NR
	Schoenmakers, 2010[197] Fair	Care counselor for regularly scheduled and ad hoc assistance	IG: 32 CG: 30	Belgium	63 (NR)	76	NR	46	NR	NR
	Spijker 2011[198] Good	Training health professionals in the systematic assessment of caregiver's sense of competence and depressive symptoms, and strategies to deal with deficiencies	IG:158 CG:143	Netherlands	59 (NR)	73	96% Dutch	28	NR (62% had mild-moderate dementia)	Minimum twice/week
	Teri 2005[199]	Home- and phone-based	IG:47 CG:48	US	65 (22–91)	70	87% White	57	13.6	NR

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Group	Study reference USPSTF quality rating	Intervention Description	n rand	Location	CG Age, Mean (range)	CG % Female	CG Race/ Ethnicity	% Spouse	Patient MMSE Score (mean)	Amount of caregiving*
	Fair	problem-solving counseling					8% Asian/ Pacific Islander 4% Black 1% Hispanic			
	Voigt-Radloff, 2011[200] Fair	Occupational therapy aimed at caregiver and patient	IG:71 CG:70	Germany	65 (NR)	71	NR	56	20.4	Minimum 2 days/week
	Williams, 2010[201] Fair	LifeSkills video modules + phone counseling	IG:59 CG:57	US	61 (NR)	78	64% White 35% Black 1% Other	41	NR	NR
	Wright, 2001[202] Fair	Management of problematic behaviors	IG:68 CG:25	US	60 (19–85)	76	69% White 31% Black	45	NR	NR
Psychoeducation + Care/Case Management	Bass 2003[203] Fair	Phone-based care consultation, providing tools to enhance patient and caregiver competence and self-efficacy	IG:109 CG:73	US	NR (NR)	NR	NR	NR	NR	NR
	Callahan, 2006[204] Fair	Primary care-based Collaborative care and psychoeducation program	IG:84 CG:69	US	61 (NR)	89	NR	45	18.1	NR
	Chu 2000[205] Fair	Comprehensive early home care program, including case management, specialty treatment as needed (physical therapy, occupational therapy, pyschiatric, etc.),	IG:37 CG:38	Canada	NR (NR)	NR	NR	NR	22.8	NR

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Group	Study reference USPSTF quality rating	Intervention Description	n rand	Location	CG Age, Mean (range)	CG % Female	CG Race/ Ethnicity	% Spouse	Patient MMSE Score (mean)	Amount of caregiving*
		respite care, other assistance								
	Eloniemi-Sulvaka, 2001[206] Fair	Comprehensive support provided by a Dementia Family Care Coordinator	IG:53 CG:47	Finland	64 (34–86)	69	NR	56	14.8	NR
	Fortinsky, 2009[207] Fair	Individualized care consultation services: problem-solving, monthly care plans sent to PCP, plus educational materials	IG:54 CG:30	US	62 (NR)	69	92% White	45	NR	NR
	REACH Memphis[185] Fair	Caregiver support in primary care + behavior management and individual counseling/support	Total n: 245	US	62 (24–89)	88	59% White 40% Black 1% Hispanic 0.8% Other	NR	11.1	Minimum 4 hours/day
	Jansen 2011[208] Fair	Case management	IG:54 CG:45	Netherlands	63 (NR)	70	NR	40	22.3	NR
	Lam, 2010[209] Fair	Case management	IG:59 CG:43	Hong Kong	NR (NR)	74	NR	29	17.8	NR
	Vickrey 2006[210] Good	Care managers provided comprehensive assessment and action plan developed with caregiver	IG:238 CG:170	US	66 (NR)	69	13% Ethnic Minority	55	NR (Dementia severity score: 6)	NR

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Group	Study reference USPSTF quality rating	Intervention Description	n rand	Location	CG Age, Mean (range)	CG % Female	CG Race/ Ethnicity	% Spouse	Patient MMSE Score (mean)	Amount of caregiving*
Assessment & Treatment Planning	LoGiudice, 1999[211] Fair	Extensive assessment and referral	IG:25 CG:25	Australia	62 (NR)	78	NR	54	NR	Minimum once/week
Computer/ Phone-based Psychoeducation	Brennan, 1995[212] Fair	Interactive computer-based information and BB with nurse moderator	IG:51 CG:51	US	60 (NR)	67	28% Black 72% White	58	NR	NR
	Finkel, 2007[213] Fair	Primarily computer-supported phone-based system based on the Miami REACH intervention	IG:23 CG:23	US	65 (NR)	68	92% White 8% Black	44	NR	Minimum 4 hours/week
	REACH Boston[214] Fair	Telephone-linked computer	IG:49 CG:51	US	63 (22–85)	88	79% White 16% Black 2% Hispanic 3% Other	NR	11.2	Minimum 4 hours/day
Family-based Psychoeducation	Joling, 2012[215,216] Fair	Psychoeducation for caregiver and family members with primary goal to increase family involvement in care and support primary caregiver	IG:96 CG:96	Netherlands	70 (NR)	70	NR	94	21.6	NR
	Mittleman, 2008[217] Fair	Individual and family counseling sessions plus donepezil	IG:79 CG:79	Australia	71 (47–88)	56	NR	NR	20.3	NR

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Group	Study reference USPSTF quality rating	Intervention Description	n rand	Location	CG Age, Mean (range)	CG % Female	CG Race/ Ethnicity	% Spouse	Patient MMSE Score (mean)	Amount of caregiving*
Peer support only	Charlesworth, 2008[218]4 Fair	Peer befriending (peer not necessarily experienced in caregiving)	IG:116 CG:120	UK	68 (36–91)	64	99% White	67	NR	Minimum 20 hours/week
	REACH Palo Alto[171] Fair	Enhanced support group	IG: 115 CG: 43	US	57 (23–90)	100	57% White 48% Hispanic	NR	13.7	Minimum 4 hours/day
	Pillemer, 2002[219] Fair	One-on-one peer support of current or former caregivers	IG: 54 CG: 61	US	58 (35–87)	71	NR	40	NR	NR
	Winter, 2006[220] Fair	Telesupport group	IG:58 CG:45	US	67 (51–86)	NR	30% Black	40.8	NR	NR
Physical activity counseling	Connell 2009[221] Fair	Telephone-based motivational interviewing for physical activity for caregivers	IG:86 CG:71	US	67 (40–87)	100	93% White	100	NR	NR
	Hirano 2011[222] Fair	Exercise prescription for caregivers	IG:17 CG:14	Japan	74 (NR)	68	NR	NR	18.3	NR
	King, 2002[223] Fair	Physical activity counseling for caregivers	IG:51 CG:49	US	63 (49–82)	100	86% White 5% Black 4% Hispanic 3% Asian/Pacific Islander 3% Cuban/White	53	NR	Minimum 10 hours/week

* From inclusion/exclusion criteria.

Abbreviations: ACT = Advancing Caregiver Training; BB = bulletin board; CDR = clinical dementia rating; COPE = Care of Persons with Dementia in their Environment; IG = intervention group; n = number; NR = not reported; OT = occupational therapist; PIC = Partners in Caregiving; PIP = Psychoeducation Intervention Program; PCP = primary care practitioner; rand = randomized; REACH = Resources for Enhancing Alzheimer's Caregiver Health; UK = United Kingdom; US = United States.

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Table 5. Caregiver Intervention Characteristics

Group	Study reference USPSTF quality rating	Primary Aim	Intervention Description	Control group	Detailed Intervention Description
Group-based psychoeducation	Belle, 2006[165] Fair	Provide comprehensive education program including support and active learning techniques to reduce caregiver burden	REACH II: Comprehensive, multicomponent psychoeducational program, including support group and computer-supported phone system	Educ materials + 2 brief phone calls	Provision of information (including resource notebook); didactic instruction; role playing; problem solving; skills training, stress management techniques; and telephone support groups to reduce risk in 5 target areas (depression, burden, self-care and healthy behaviors, social support, problem behaviors) by providing caregivers with education, skills to manage troublesome patient behaviors; social support; cognitive strategies for reframing negative emotional responses; strategies for enhancing healthy behaviors and managing stress. Individualized to participant based on baseline assessment.
	Brodaty, 1989[166] Fair	Reduce distress and improve QOL for both pt and cg	10-day residential education, training, and support program for cg and pts, 10d memory tng program for pts	CG1: pt 10d residential memory tng program, no cg intervention; CG2: pt 10d residential memory tng program + 6m Waitlist for cg program	Dementia carers' program (caregivers). 10d residential stay for cg and pt plus phone-based followup. The program was aimed at alleviating difficulties associated with being a carer of a person with dementia. Specific targets: psychological distress; isolation and lack of support; lack of assertiveness and apprehension about new roles; poor marital relationship; lack of info about dx, mgmt, progrnosis, domiciliary, and welfare services; legal and financial matters; home safety and organization. The techniques used in the program included didactic education, group therapy, training in management skills, assertivenss training, discussion of "re-roling," extended family therapy sessions, training in techniques for managing problems, basic principles of behavior modification, and use of activities. Telephone calls linking the caregivers every 2w immediately after inpat program, then decreasing in frequency to every 6w. Plus additional CG program for pts: 10d residential stay for memory retraining, reminiscence therapy, environmental reality orientation, general ward activities, med/psych review + tx as warrented.
	Burgio, 2003[167] Fair IV rec'd in 1st 6m, when only outcomes are reported		REACH-Birmingham: Psychoeducational and skills training program	10 15-min supportive phone calls and educational	Workshop with instructional activities to encourage sharing among caregivers. Caregivers were also provided with a skills training notebook and videotapes that demonstrated critical skill techniques. A TV-VCR was lent if caregivers

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Group	Study reference USPSTF quality rating	Primary Aim	Intervention Description	Control group	Detailed Intervention Description
				materials	needed one. Caregivers were also visited by a REACH interventionist who assisted them in the application of therapeutic skills. Caregivers received therapeutic phone calls to further refine skills. Caregivers received basic information on behavioral management techniques as well as instruction and support in the technical appliction of specific behavioral and environmental treatments. Caregivers were given specific instructions in the application of problem-solving. Therapists also used cognitive restructuring. Designed to be culturally appropriate for African American and White caregivers.
	Chu, 2011[168] Fair	Reduce caregiver burden and depression	Group education program	UC	Introduction to the support group process covering the group's goals, objectives, rules, expected behaviors, and asking caregivers to tell their story. The second and third sessions, the caregivers' emotions and feelings about caregiving were openly discussed; the fifth and sixth sessions were focused around the patients' reactions and common behaivor problems. Sessions 6 and 7 addressed caregiver's need to take care of themselves and to do positive things with the dementia patient; 8 and 9, caregivers were informed about the availability of community resources, discussed financial issues and in-home services. Sessions 10 and 11 communication problems were the main focus. Final session, group progress was reviewed and caregivers were assisted to develop future plans for care.
	Coon, 2003[169] Fair	Reduce psychological distress, improve positive coping and caregiving self-efficacy	IG1: Psychoeducational and skill training with anger management	WL + brief calls to increase retention	Psychoeducational and skill training in nature, teaching and helping caregivers practice distinct self-management skills. IG1 covered anger management (relaxation techniques, self-monitoring, positive self-talk, assertiveness skills, including role-playing and rehearsing) and IG2 covered depression management (learn about connection between mood and pleasant events, monitor and increase pleasant events, problem-solving to overcome obstacles).
	Coon, 2003[169] Fair	Reduce psychological distress, improve	IG2: Psychoeducational and skill training	WL + brief calls to increase	Psychoeducational and skill training in nature, teaching and helping caregivers practice distinct self-management skills. IG1 covered anger

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Group	Study reference USPSTF quality rating	Primary Aim	Intervention Description	Control group	Detailed Intervention Description
		positive coping and caregiving self-efficacy	with depressions management	retention	management (relaxation techniques, self-monitoring, positive self-talk, assertiveness skills, including role-playing and rehearsing) and IG2 covered depression management (learn about connection between mood and pleasant events, monitor and increase pleasant events, problem-solving to overcome obstacles).
	de Routrou, 2011[170] Fair	Improve psychological status of caregiver and patient's activities of daily living	Comprehensive group psychoeducation	Wait list	In every session, experienced health professionals provided caregivers with detailed information on specific aspects of the disease. The program was focused on education, problem-solving techniques and emotion-centred coping strategies, management of patient's behaviour, communication skills, crisis management, resource information and practical advice. Caregivers gave their feedback on events of the previous week. Solutions raised from individual experiences had to emerge from the group rather than provided by the coordinator. During the last 20 min, carers were explained how to stimulate their relative in daily activities and social situations in an ecological and individual tailored way, according to personal interests. At the beginning of each session, caregivers gave their feedback about the way they had managed their difficulties in the previous week.
	Gallagher-Thompson 2003[171] Fair	In cgs, reduce depressive sx, increase use of positive coping strategies, decrease use of negative coping strategies, and be less bothered by pt behavior	REACH Palo Alto: Coping with Caregiving class.	Educational materials + brief supportive phone calls (number NR)	IG1 (Coping): Coping with Caregiving class. Psychoeducational class developed to teach a limited number of cognitive-behavioral mood management skills through 2 key approaches: first, an emphasis on reducing negative affect by learning how to relax in a stressful situation, appraise the patient's behavior more realistically, and communicate more assertively; and second, an emphasis on increasing positive mood through the acquisition of such skills as seeing the contingency between mood and activities, developing strategies to do more small, everyday pleasant activities, and learning to set self-change goals and reward oneself for accomplishments along the way. Also given 2 packets of materials.
	Gallagher-Thompson, 2008[172] Fair	Reduced stress and depressive symptoms through	Cognitive-behavior program on coping with caregiving	Telephone support (7 15-20m calls over	Coping with Caregiving. Based on cognitive-behavioral principles; it is a skills-learning based approach and included opportunity fo practice and

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Group	Study reference USPSTF quality rating	Primary Aim	Intervention Description	Control group	Detailed Intervention Description
		improved cog and behavioral skills		4m) + educ materials	for personalization of material at each meeting. Caregivers discusses experiences and problem-solving is done to address barriers.Short discussions in private if needed. Mini lecture to introduce the rationale for a new strategy or continue to discuss an old strategy if needed. Strategy is practiced through role-playing and other forms of engagements. Relaxation techniques. Final class had caregiver develop an action plan for how to apply strategies to anticipated stressful situations. Topics covered: educ about dementia, neg effects of stress on body and mind, how to identify and track problem behaviors, techniques for managing problem behaviors and identifying antecedents, cognitive restructuring, assertive communication, increasing pleasant events, planning for future, community resources.
	Hebert, 1994[173] Fair		Group psychoeducational program	refered to Alzheimer's Society support group	In the first session, the program is presented, the participants are introduced, and the specific needs of each participant are defined. Participants are invited to establish priorities according to their needs in caregiving and their emotional reactions. The other sessions are divided into 3 parts: information on dementia is presented (sx, dx, tx, resources available, legal and ethical issues; role-playing; relaxation techniques.
	Hepburn, 2001[174] Fair	To improve caregiver outcomes by teaching caregivers to frame their role as caregiver in more clinical, strategic terms, eg as a job	Minnesota Family Workshop	WL	Minnestoa Family Workshop. Classroom instruction and exercises along with assignments to read additional material and to put into practice principles and strategies taught in the workshop. Included 5 components: information provision, concept development (understanding progressive effect on pt and guided in developing stage-specific strategies for managing daily life and behavior), role clarification (pt's security and comfort, not rehab or changing the course of the disease), belief clarification (including importance of self-care) and impact of their emotions on pt, mastery-focused coaching. Daycare for pts while cg in training sessions.
	Hepburn, 2005[175] Fair	Mediate the impact of stressors by strengthening the	Partners in Caregiving (PIC) program, focus on		Partners in Caregiving (PIC) program. The curriculum emphasized mastery of the practice of daily caregiving and development of a confident

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Group	Study reference USPSTF quality rating	Primary Aim	Intervention Description	Control group	Detailed Intervention Description
		carefiver's abilities to undertake and succeed in caregiving	day-to-day caregiving (IG1) or decision-making framework IG2), but groups combined for results		caregiving attitude. Taught caregivers to develop strategies for dealing with disease's impact. Taught to use activity analysis framework to strengthen caregiver's ability to fit daily tasks and activities to pt's capacities. Demonstrated behav mgmt techniques to cg. Homework and practice skills and strategies between sessionss. Follow-up coaching emphasized skills like assessing the immediate situation, brainstroming and implementing solutions, evaluating results. The PIC consisted of 2 versions of a multi-session multidisciplinary program. The basic program focused on day-to-day caregiving (IG1). The second version placed caregiving practice in a decision-making framework, identifying and using values and preferences as a way to evaluate the options available in day-to-day caregiving decisions (IG2). Groups combined for analysis.
	Kurz, 2010[176] Fair	Improve mood and QOL of cgs	Group education program	UC (for Austria, Switzerland, or Germany)	The educational program focused on information about Alzheimer's disease and was structured for the different stages of dementia severity, but allowed for flexibility in dealing with individual problems. The bi-monthly sessions targeted individual needs or problems. Session content covered general information about Alzheimer's, and information specific to different stages of the disease; behavioral strategies for handling challenging behavior; issues of intimacy and role change; legal and insurance-related issues, seeking support.
	Losada, 2010[177] Fair	Reduce caregiver depression through modifying dysfunctional thoughts and increasing behavioral activation	Group caregiver training	Usual care (for Spain) or assistance by social and health centers	The intervention was aimed at training caregivers in techniques and skills to acknowledge, analyse, and flexibilize maladaptive thoughts. Specifically, cognitive barriers to self-help and to do pleasant activities were sought and analysed. All the sessions presented the same structure: (a) the initial 20 and 30 min were devoted to the analysis and discussion of home work; (b) the following 20–30 min were dedicated to the exposure or description of basic concepts to be worked out (e.g. what is a thought, the relationship between situation, thought and emotion, etc.); and (c) the rest of the time involved the performance of

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Group	Study reference USPSTF quality rating	Primary Aim	Intervention Description	Control group	Detailed Intervention Description
					exercises and the practice of basic cognitive and behavioral techniques and skills (e.g. analyzing in graphs the relationship between reported mood and number of pleasant activities done through the past week; analyzing registers of thoughts and their relationship with feelings and the situations that generated the feelings, etc.). Basic principles for caring for a relative with dementia (e.g. security and basic strategies for promoting independence in their relatives' behavior) were also covered.
	Ostwald, 1999[178] Fair	Reduce behavior problems in pts, reducde burden, depression, and negative reactions to pts in cgs	Multifaceted curriculum delivered via lectures and video	WL + info packet about community resources	Multifaceted curriculum to provide caregivers and family members with information about dementing diseases and how they affect persons with dementia, caregivers, and family as a system; develop and strengthen caregivers' practical skills for dealing with caregiving tasks on a day-to-day basis; strengthen caregivers' feelings of confidence and belief that they are able to deal with issues; improve family communication and cooperation. Also received a packet of information about resources available in the community for Alzheimer's care. Included classroom exercises, readings, and homework. Engaged other family members throughout. Patients with dementia were invted to attend concurrent group (day care-like activities and testing). Sessions typically included 5 primary caregivers and 8-10 other family members.
	Signe, 2008[224] Fair	Improve cg burden and satisfaction	Group education and support	UC (in Scandinavia)	General education with group discussion, strategies to mobilize help, for reducing isolation, and for coping or overcoming difficulties. Session content included information about dementia, resources and services available in the community, planning for the future, communication with ppl with demential, promoting positive attitudes toward peple with dementia, coping with challengting behavior, developing new skills and knowledge, and taking care of yourself. Written information at the end of the intervention, including a page with useful telephone numbers. Familty caregivers could continue with the conversation group. They were given practical and emotional support and the leader tried to clarify the needs of the caregivers and to help them find the kinds of support they

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Group	Study reference USPSTF quality rating	Primary Aim	Intervention Description	Control group	Detailed Intervention Description
					were looking for.
	Ulstein, 2007[179] Fair	Reduce caregiver stress and improve behavioral and neuropsychiatric sx in pts	Group education program	UC (for Norway memory clinic)	Educational program. Carers are taught about symptoms and the normal course of dementia and about pharmacological and nonpharmacological treatment. Group sessions taught communcation techniques and structured problem-solving. The focus was on how to handle neurpsychiatric symptoms, how to get more informal and professional assistance and how to encourage the patient to accept this kind of help. Cognitive techniques were used to help the carers have more realistic expectations about the patients' functioning in everyday life and to make them understand the behavioral changes of the dementia syndrome.
	Waldorff, 2012[180] Good	Prevent emergence of depression and improve quality of life for patients and caregivers	Group courses targeting caregiver and patient plus individual sessions for dyad	At the assessments at six and 12 months, the raters were instructed to accommodate the patient's and carers' typical frustration and uncertainty associated with a recent diagnosis by providing overall information and guidance, and they could facilitate contact to relevant local support programs in both the control group and the intervention	The DAISY intervention was conducted as a supplement to the control support. It was tailored individually to each of the participating dyads, and it offered the participants a number of components at their disposal. Up to seven counselling sessions were scheduled: two sessions with the patient and caregiver; two sessions with the patient alone; two sessions with the caregiver alone; and an optional network session with the patient, caregiver, and family network. The counsellor offered the participants guidance with common decision making, advice, and activities that help the participants construct a meaningful life. Written notes were used to focus follow-up sessions with the aim of improving coping strategies and empowering the participants to focus on the positive factors and resources in their lives, according to the principles of self validation. Two parallel lines of five courses each were targeted at patients and caregivers respectively. The objective of the courses was to provide a basic knowledge about the disease and its consequences along with establishing a forum for patients' and caregivers' exchange of experiences and coping strategies. The study coordinator contacted the participants by telephone about five to eight times at three or four week intervals. The calls focused on issues discussed at the individual sessions and education courses, but sometimes the conversations included

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Group	Study reference USPSTF quality rating	Primary Aim	Intervention Description	Control group	Detailed Intervention Description
				group.	other issues relevant for the individual participant. Patients and caregivers were also supplied with comprehensive written information to support the information given at counselling sessions and courses and a log book in which they could write information and thoughts about their daily life.
Individual psychoeducation	Chang, 1999[181] Fair	decrease cg burden, improve cg mental health, and prevent or delay nursing home placement for pt	Video-based information and phone counseling	Weekly supportive calls assessing cg general well-being	Videotapes demonstrating assisted modeling behavior (eating and dressing) and a support program to reinforce the vidoes and assist the caregiver to explore coping strategies.
	Ducharme, 2011[182] Fair	Improve caregiving and self-efficacy related to caregiving	Individualized counseling and education program	UC at memory clinics	7 modules: caregiver perceptions of the care situation; coping strategies for dealing with difficulties and averting psychological distress; how to communicate and enjoy time spent with the patient; how to use strengths and experiences to take care of the patient; how to get friends and family to help; knowledge of services and how to ask for them; and planning ahead for the future. Specific skills include communication skills, discussing responsibility for care among family members, becoming familiar with available resources, planning for the future. Includes workbook with documents and exercises to put session topics into practice.
	Gitlin 2008[183] Fair	Reduce behavioral disturbance in pts and burden in cgs	Tailored activity program: identify and capitalize on preserved pt abilities	WL	Interventionists met with caregivers, introduced intervention goals, used a semi-structured interview to discern daily routines, and identified previous and current activity interests. Interventionists observed dyadic communication and home environmental features and assessed dementia patients using the Dementia Rating Scale and Allen's observational craft-based assessments. Interventioniosts identified 3 activities and developed 2-3 page written plans (Activity Prescriptions) for each. Each prescription specified patient capabilities, an activity and goal and specific implementation techniques. The prescription was reviewed and the activity introducted through role play or direct demonstration. Caregivers were also instructed in

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					stress reducing techniques to help establish a calm emotional tone. Caregivers learned to generalize approach for reducing complexity of tasks.
	Gitlin, 2001[184] Fair	Examine short-term effects of home environmental intervention on self-efficacy and upset in caregivers and daily function in dementia patients	Targeted multi-component program by occupational therapists	Educ materials at the end of the study	Targeted, multicomponent program focusing on home environment. Therapist met with caregiver to develop a targeted plan that addressed the specific aspects of daily care that were problematic and for which the caregiver wanted to learn new strategies. Education about the disease process and impact of environment on dementia patients, and benefits of environmental simplification and breaking down tasks for pts. Role-play, direct observation and interviewing to explore ways in which the caregiver handled problem areas and conceptualized or cognitively framed their situation. Education about dementia and the role of the physical and social environment was presented in relation to the specific care difficulties presented by caregivers. The therapists engaged caregivers in mutual problem solving to identify alternate care strategies. Therapist reinforced education about dementia through written materials and discussion, addressed a targeted problem area, observed the caregiver using previously recommended strategies, and/or offered new recommendations.
	Gitlin, 2003[185] Fair	reduce burden and improve QOL in cgs through modifications to the pts environment	REACH Philadelphia: Environmental skill-building program	UC + educational materials	Environmental skill-building program. Educate caregivers about the impact of the environment on patients. Provides caregivers with the skills and technical support necessary to alter their home environments in order to help reduce the adverse impact of behavioral problems. The OT reviews intervention goals and conducts a systematic needs assessment to identify which of 11 areas are difficult for the caregivier to manage and for which he/she wants to learn new strategies. 11 domains considered: caregiver-centered concerns, communication issues with the patient, problems in coordinating care, difficulties assisting in ADLs, concern about home safety, difficulty distracting or engaging patient, concern with wandering, difficulty managing incontinence, difficulty managing catastrophic reactions. In the second visit, the OT continues the education process and works with

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					the caregiver to problem solve about antecedents and consequences of a particular identified problem area. In each susbsequent visit, the OT reinforces education about dementia through written materials and discussion, addresses a targeted problem area, observes the caregiver using previously recommended strategies, provides refinement, and offers new recommendations. Strategies may include modifications to the physical environment, strategies to simplify pt task completion (e.g., simplifying task, providing cues), modification to the social environment (coordinating care among social network, communicating with providers).
	Gitlin, 2010[187] (ACT) Fair	Help caregivers eliminate, reduce, or prevent problem behaviors by identifying and modifying potential triggers for problem behaviors.	ACT: Occupational Therapy invervention	No OT contact	IG: OTs met with caregivers to introduce intervention goals, review targeted problem behaviors identified at BL, and observe home environment for patient way-finding and potential hazards (e.g. placement of medication) and caregiver-patient interactions (e.g., communication style) using standardized checklists. An action plan was provided. Caregivers were instructed in stress reduction and self-care techniques. Skills were built by having caregivers practice problem-solving and strategy identification and use with OTs and then independently between sessions. Stress reduction and self-care were covered. Low-cost assistive devices were provided. An advanced practice nurse met with caregivers to provide education on common medical conditions that may exacerbate problem behaviors. Patient medications were reviewed and possible undiagnosed illnesses were tested for.
	Gitlin, 2010[188] (COPE) Fair	improved alignment of environmental demands with patient capability will improve patient and caregiver outcomes	COPE: Occupational Therapist assessment, education, and training	Educ materials + 3 20m phone calls	IG: Assessments (patient deficits and capabilities, medical testing, home environment, caregiver communication, and caregiver-identified concerns); caregiver education (patient capabilities, potential effects of medications, pain, constipation, dehydration); and caregiver training to adress caregiver-identified concerns and help them reduce stress. Included training in problem-solving, communication, engaging patients in activities, and simplifying tasks.

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	Hebert, 2003[190] Fair	Reduce caregivers' reactions toward troublesome behaviors and indirectly reduce their burden, psychological distress, and anxiety, and improve their perception of social support and well-being	Cognitive appraisal and coping strategies group psychoeducational program	refered to Alzheimer's Society support group	First component was cognitive appraisal, with the primary objective of improving the caregiver's ability to shift from a global stressor to a specific stressor (i.e., break down to specific elements to clarify the problem and increase awareness that something can be done. Second and third objectives were to develop the caregivers' ability to distinguish between the changable and unchangable aspects of a stressor and their awareness of the importance of the match between the changability of the stressor and choice of coping strategies. Homework to practice identifying specific stressors and identifying changeable and unchangeable aspects and emotional reactions. Second component was coping strategies; mainly focused on problem-solving, reframing, and seeking social support
	Hinchliffe, 1995[191] Fair	reduce behavioral disturbance in pts and improve mental health of cgs	Individualized care package	WL	Individualized care package for each patient and caregiver. Medication, psychological techniques, and social measures were considered. 3 lines of approach were taken to reduce the frequency and/or duration of specified behaviors; reduce caregiver exposure to the behavior; and improve the caregiver's ability to cope with the behavior.
	Huang, 2003[192] Fair	Reduce problem behaviors in pts, improve cgs self-efficacy for mgmt of problem behaviors, and improve environmental supports for cg	Individualized counseling and education program	written materials and biweekly social phone calls	2-session in-home training program. At the initial visit, the investigator established a partnership with the family caregiver by working through a structured assessment guide. Assessments were made on the conditions of the dementia patient, including habits, daily routines, preferences, behavioral problems and environmental safety and stimulus. Then the investigator worked with the family caregiver to identify targeted behavioral problems and explored causitive environmental stimuli. A tentative plan to minimize the stimuli by modification of the daily schedule was then made with the family caregiver. A second visit was mde to further assess family resources, confirm the behavioral problems, and finalize the plan for handling specific behavioral problems with the caregiver. Contact information for investigator was left in case of problems. Followup phone calls.

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	Marriott, 2000[193] Fair	Reduce caregiver burden	Individualized counseling and education program	CG1: UC (for UK) CG2: UC (for UK) plus In-depth interview	3 main components: carer education, stress management, and coping skills training. Carer education: Caregiver's knowledge of dementia was thoroughly assessed (3 sessions); general information on Alzheimer's diease and practical advivce and management was provided. Stress management (6 sessions): Assessment of caregiver's current appraisal and response to stressors. Adaptive methods of managing personal stress were taught, including self-monitoring, relaxation training, and cognitive and behavioral responses. Training in coping skills (5 sessions): Advice about and role-play of more effective ways of responding to problematic patient behaviors, and exercises to address caregiver's feelings of loss concerning changes in the patient or alterations to their own quality of life. 4 booklets were given that covered information about AD, the intervention topics and available services. Audio-taped in-depth interview same as CG1.
	Martin-Carrasco, 2009[194] Fair	Reduce caregiver burden	Psychoeducation Intervention Program (PIP)	UC (for Spain)	Usual care (for Spain) as well as a Psychoeducational Intervention Program (PIP) where information was provided about the disease and the caregivers were taught to control tension and stress deriving from the caregiving and also strategies for handling patient's behavioral problems and increasing their satisfaction with life. Incorporated elements of cognitive-behavioral counseling, including control of activation (assume this is behavioral activation), cognitive restructuring techniques, problem-solving, and increasing rewarding activities
	Martin-Cook, 2005[195] Fair-	Increase cg sense of competence and reduce depression sx by helping cgs develop a more realistic view of pts function	Individualized training program to help cgs accurately assess pts functioning and demonstrate simplifying tasks	WL + info about community resources	Individualized based on the functional level of the patient and the coping level of the caregiver. Four weekly skills training sessions where caregivers progressed from observer to active participant. Taught caregiver to test functional abilities, break down ADLs to simpler tasks and provide other visual, auditory, tactile, or multimodal cue to improve functioning. Individualized suggestions to enhance communication and specific strategies to facilitate cueing on ADL were reviewed. Practical advice regarding home safety and information

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					about community resources, companion service agencies, and other home health services was offered.
	Roberts, 1999[196] Fair	Reduce psychological distress, durden, and expenditures for health and social services, and improve social support and coping methods	Problem-solving counseling	Usual community and respite services (for respite nursing agency in Canada)	3 community nurses were trained in problem-solving therapy by experienced therapy nurses; a problem-solving manual was used. Thes nurses provided individual sessions to relatives. Relatives also received usual ongoing available community and respite services by other nurses and volunteer agencies.
	Schoenmakers, 2010[197] Fair	Improve patients functioning in daily life activities and cognitive function	Care counselor for regularly scheduled and ad hoc assistance	Not guided or visited by the care counselor but were passively directed to the usual care systems (for Belgium)	The care counselor was at the exclusive disposal of the intervention group. Over a course of 12 months, the care counselor guided the family carer in organizing home care. At a first visit, the counselor assisted the family carer in exploring any problematic home care situations. Additionally, the care counselor arranged a monthly phone call with the family carer and a three monthly visit. During the intervention period twelve phone calls and four home visits were scheduled. Additionally, the care counselor was within permanent reach for advice by phone, for adjusting home care or for an extra visit. No structured or hierarchical care plan was provided but drawn out following the needs of the family carer and patient. General practitioners were informed about each change in formal or informal home care of their patients.
	Teri, 2005[199] Fair	Reduce depression, burden, and stress in cgs and improved mood, decreased behavioral disturbance, and improved QOL in pts	Home- and phone-based problem-solving counseling	UC (in US)	Consultants met with caregivers in their homes, followed by phone calls. The first 3 sessions focused on teaching caregivers the rationale and use of the A-B-C problem-solving approach to behavior change. Using examples from the caregiver's weekly diary, the caregiver and consultant brainstormed strategies for modifying antecedents or consequences of problem behaviors, and developed written behavior-management plans for the following weeks. Subsequent sessions focused on improving caregiver communication, increasing pleasant events as a means to improve patient's mood, and developing strategies to enhance caregiver

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					support. In the followup phone calls, consultants helped caregivers develop behavior management communcation, pleasant-event and caregiver support strategies for any new problem that arose.
	Voigt-Radloff, 2011[200] Fair	Improve daily functioning of pts; improve cgs QOL, mood, and competence; delay long-term nursing home placement	Occupational Therapy aimed at caregiver and patient	single 1/2- to 1-hour session with OT covering leaflet and answering questions	Dutch 10-session community occupational therapy dementia program, delivered in patient's home. OT explored the patient's preferences and history of daily activities; their ability to perform activties and use compensatory strategies within the familiar environment; the possibilities of modifying the patient's home; the caregiver's activity preferences, problems in caregiving, coping strategies and abilities to supervise; the interaction between caregiver and patient. The caregiver and patient selected the 1-2 most meaningful activities out of a list of their preferences for daily activities to work on. The OT, patient and caregiver defined more effective compensatory and environmental strategies, activities and environment in order to improve their performance of daily activities. The caregivier received practical and emotional support and was coached in effective supervision, problem-solving and coping strategies.
	Williams, 2010[201] Fair	reduce cg stress through acquisition of skills	LifeSkills video modules + phone counseling	WL	LifeSkills video modules: increasing awareness of and objectivity in distressing situations; evaluating one's reactions to those situations to decide whether to try to change one's reactions or to take actions to try to change the situations; changing one's reaction to distressing situations; using assertion to get others to change their behavior; problem solving to change distressing situations; saying no to reduce exposure to distressing situations; speaking clearly so others really listen; listening skills to make sure you hear what others are saying; empathizing to increase understanding of other's behavior; increasing the positives in your interactions with others. Videos were accompanied by a workbook that provided additional information. Phone calls to facilitate modules, apply video material to cg's specific situation.
	Wright, 2001[202] Fair	reduce agitation and institutionalization	Management of problematic behaviors	No behavior management program	Caregivers were asked to identify the most troublesome behaviors in the patient. Strategies for handling such behaviors as hiding and hoarding of

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		in pts, reduce depression, stress in cgs through improved behavior management and medication monitoring of pts			objects, repetitive questions, or restlessness were discussed, and a plan for the caregiver to implement a new approach was developed. In addition, the patients' medications were monitored. If side effects were noted or a dosage adjustment seemed indicated, the clinical nurse specialist conferred with a physician. The caregivers' emotional and physical health was addressed with supportive counseling. Caregivers were encouraged to openly express anger, frustrations, and sadness. Strategies for getting help were discussed. Referrals to home health agencies, support groups, and other AD programs were made, and intensive psychotherapy if needed. Physical health concerns were discussed and medical referrals made if needed.
Psychoeducation & Care/Case Management	Bass 2003[203] Fair	Care consultation will have beneficial effects on health care utilization, caregiver satisfaction with services, and caregiver depression and care-related strain	Phone-based care consultation, providing tools to enhance pts and cg competence and self-efficacy	Can contact Alzheimer's Association independently	Flexible, multicomponent intervention. It is a telephone intervention based on an empowerment conceptual framework. Care consultants work with families to help identify personal strengths, as well as resources within the family system, health plan, and community. the goal is to provide tools to enhance patients' and caregivers' competence and self-efficacy. Care consultants also provide information about available community services, facilitate decisions about how best to utilize and apply for these services and may contact service agencies on behalf of the caregivers and patients.
	Callahan, 2006[204] Fair	Improvement in neuropsychiatric functioning of AD pts	Primary care-based Collaborative care and psychoeducation program	"Augmented" UC (written materials, 40-90m counseling session w geriatric NP, dx write-up to PCP from NP	Collaborative care management for a maximum of 12 months. Recommended for treatment with AChEIs or memantine unless contraindicated. Education on communication skills, caregiver coping skills, legal and financial advice, patient exercise guidelines with guidebook and video, and caregiver guide provided by local Alzheimer's Association. Individualized recommendation for managing difficult pt behavior and specific stressors. Specific protocols developed for: personal care, repetitive behaviors, mobility, sleep disturbances, depression, agitation or aggression, delcusions or hallucinations, and caregiver physical health. Care manager also used a web-based tracking system to manage pt appointments and for

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					communicating pt status to treatment team. Met with treatment team members to plan and evaluate treatment. Invited to participate in voluntary support group sessions focused on support and stress mgmt (caregivers) and chair-based exercise (patient). Also received the same intervention components as the CG.
	Chu 2000[205] Fair	reduce cg burden and delay institutionalization	Comprehensive early home care program, incl case mgmt, specialty tx as needed (physical therapy, OT, pyschiatric, etc.), respite care, other assistance	Information on community resources	Early Home Care Program. Provided case mangement, occupational therapy, physical therapy, social work, nursing, respiratory therapy, in home respite, and out-of-home respite, homemaking, personal care assistance, volunteer service and psychiatric consultation. Objectives were to assist the clients and family to: initiate long-term planning early related to issues such as housing, finance, legal matters, caregiving support; increase use of the home care and otehr community services; improve the coping strategies related to psychosocial issues which often hinder long-term planning and service utilization; improve caregiving strategies related to functional and behavioral difficulties of the individuals with AD.
	Eloniemi-Sulkava 2009 [225] Good	delay institutionalization and reduce healthcare utilization and costs	Comprehensive support provided by a Dementia Family Care Coordinator	UC (for Finland)	The core elements of the intervention consisted of a family care coordinator's (FCC) actions, a geriatrician's medical investigations and treatments, goal-oriented support group meetings for caregivers and individualized services. All the coordinated services were planned in collaboration with the families. At a home visit with the FCC an initial support plan was created. The geriatrician's appointments and comprehensive geriatric assessments and treatment for the patients (or caregivers if needed) followed the visit. The services were primarily arranged through the municipal social and healthcare system. The FCC operated in partnership with the geriatrician, who was available to the couples. The caregivers participated in 5 goal-oriented support group meetings during the first year. Each meeting had a different theme relevant to caregiving.
	Eloniemi-Sulvaka, 2001[206] Fair		Comprehensive support provided by a Dementia Family		Comprehensive support provided by a DFCC, who had access to a physician. The DFCC gave continuous and systematic counseling, conducted

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			Care Coordinator		follow-up calls and in-home visits as well as arranging social and health care services. She acted as a dementia expert and an advocate for the patients and the caregivers. Only services in the financial range of the caregivers and patients were used. Both the patients and caregivers participated in annual courses. The purpose of the courses was to support the functional capacity and adaptation of both patients and caregivers (included medical check-ups, psychological assessments, lectures, therapeutic group meetings, and different kinds of physical, mental, and social stimulation). The rehabilitation team made the service plan for each family.
	Fortinsky, 2009[207] Fair	Prevent/delay nursing home admissions by improving knowledge and psychosocial outcomes and increasing use of available services	Individualized care consultation services: problem-solving, monthly care plans sent to PCP, plus educational materials	Educ materials only	Received a package of educational materials at baseline related to dementia symptom management and available community services. At monthly meetings it was determined which aspects of dementia symptoms and care responsibilities caused caregiver concerns, discuss action steps to address caregiver concerns, and compose a written care plan. Each care plan was organized according to problems or concerns expressed by the family caregiver (whether related to the caregiver or patient), along with action steps that caregivers should take to address each concern. The minimum care plan for all family caregivers included the action steps that family caregivers should take to learn more about or use; key information about the clinical course of the disease process; legal and financial planning issues; family support groups; dementia educational programs offered by the chapter and other organizations; adult day care services; and respite care services. Care plan was also faxed to patient's physician with the expectation that the physician would review the care plan with the caregiver, inquire if action steps had been taken, and reinforce the importance of the plan.
	Gitlin, 2003[185] Fair	reduce stress in cgs	REACH Memphis: Caregiver support in primary care + behavior	Information during 4-6 primary care visits and	Behavior care. Caregivers are taught personal strategies to help themselves cope better when problem behaviors arise. Supplemental telephone calls between office visits help extend face-to-face

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			management by phone	referral to local Alzheimer's organizations	meetings by providing caregivers the opportunity to further review and discuss intervention materials. Caregivers receive specific handouts identified through the in-person counseling sessions.
	Gitlin, 2003[185] Fair	reduce stress in cgs	REACH Memphis: Caregiver support in primary care + behavior management and individual counseling/support	Information during 4-6 primary care visits and referral to local Alzheimer's organizations	IG2: Enhanced care. In addition to IG1, enhanced care teaches specific stress and behavior management strategies for the caregivers themselves through face-to-face meetings with the interventionists at regularly scheduled primary care office visits. Enhanced care educates caregivers on successful cognitive and behavioral strategies that can help change negative thinking patterns and may also help reduce caregiver distress in caregiving situations where the course of events cannot be altered.
	Jansen 2011[208] Fair	improve compentence, psychosocial functioning, and QOL in cgs, and QOL in pts	Case management	UC (for The Netherlands)	Case management entails assessment, planning, coordination, collaboration, and monitoring of care. Nurses provide practical, informational and socioemotional support. Multiple support strategies are offered to informal caregivers and patients (e.g., support groups, respite care). The intervention begins with a home visit in which they administer the Resident Assessment Instrument Home Care (RAI-HC). The nurses and participants order the identified problems into a heirarchy and formulate a care plan for these problems. They leave behind a form to register care received and appointments with health professionals. In the 2nd home visit, the nurses explore the caregiver's situation with a capacity and burden questionnaire and hand a guide to caregivers holding available social services and welfare professionals. Additional visits are planned as needed. Nurses contact and monitor the situation at least every 3 months. Nurse contact the GPs to inform them about the situation.
	Lam, 2010[209] Fair	Reduce burden of cgs of older people with mild dementia	Case management	UC (for Hong Kong)	Subjects were assigned to a case manager (OT). Assessment and advice: The case manager evaluated the activities of daily living and neuropsychiatric symptoms of the demented subjects, and caregiver distress in care duties. Advised caregivers and patients on safe performance in basic self-care activities with

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					environmental modification to promote safe home living, behavioral management, and communication techniques. Home-based program on cognitive stimlation: Training on home-based cognitive stimulation strategies that included reading newspapers together, reminiscence by old-time photos, continued engagement in usual household tasks and leisure activities. Reinforced by home visits and telephone calls. Case management: Support to caregivers and patients by home visits initially, later by phone calls, and follow-up at hospital clinic visits. Encouraged the subjects to be registered with local social centers. Liased with staff in the social centers to ensure smooth integration. The case manager was accessible by a telephone hotline during working hours Monday-Saturday. Liased closely with the psychogeriatricians or geriatricians in the clinics.
	Vickrey 2006[210] Good	Improve adherence to dementia guidelines	Care managers provided comprehensive assessment and action plan developed with caregiver	UC (in US)	23 existing dementia guideline recommendations were selected as care goals by a steering committee (a physician from each health care organization, a leader from each community agency, a community caregiver, and investigators). The committee also designed a structured assessment, algorithms linking specific care management actions to assessment results, and interorganization care coordination and referral protocols. Every enrolled patient and caregiver dyad was assigned a care manager who contacted them to schedule a structured home assessment. The care manager collaborated with the caregiver to prioritize problem areas; teach problem-solving skills; initiate care plan actions; and send and assessment summary, a problem list, and selected recommendations to the PCP and other designated providers. A meny of potential care plan actions was documented. The care manager provided ongoing followup.

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Assessment & Treatment Planning	LoGiudice, 1999[211] Fair	Improve psychosocial health status and reduce burden of cg	Extensive assessment and referral	Assessment only, questions raised were answered and referral back to GP was encouraged	Attended a hospital memory clinic on 2 occasions. The initial visit included a complete medical and cognitive assessment. Principal carers were interviewed by the research nurse who provided advice and counseling as well as completing the CAMDEX informant interview schedules. Participants were invited back for a neuropsychological assessment. A family conference was undertaken with carers, patient, and family members to discuss the details of the outcomes of the assessment. Participants were free to ask questions and a plan of assistance was formulated, which included referral to appropriate services. GPS were informed of the assessment.
Computer/ Phone-based Psychoeducation	Brennan, 1995[212] Fair	reduce social isolation in cgs and improve decision-making skill and confidence	Interactive computer-based information and BB with nurse moderator	NR, assume UC	ComputerLink. Included a public bulletin board, private email, and a question-and-answer segment facilitated by a nurse. It included a 4-module electronic encyclopedia on Alzheimer's disease and its treatment, management of symptoms, services for Alzheimer's patients and caregivers, and self-care for caregivers. Also included a decision-support module that helped caregivers address unsolved problems and dilemmas.
	Finkel, 2007[213] Fair	See if technology-based intervention is feasible for social service agency	Primarily computer-supported phone-based system	Educ materials + 2 brief phone calls	Focused on provision of information about the disease and community sources and strategies to enhance safety, communication, self-care, social support, and management of problem behaviors. A computer-telephone integration system (CTIS) was the primary vehicle for intervention delivery and the intervention was delivered by staff at the Council for Jewish Elderly. The CTIS system involved the use of screen phones that allowed the users to place/receive calls, send/retrieve messages, access a range of information and services, and conference with several people simultaneously. Each caregiver was provided with a phone.
	Mahoney 2003[214] Fair	reduce stress, depression, and anxiety in cg through reducing pts disruptive behaviors	REACH Boston: Telephone-linked computer.	UC + educational materials	Telephone-linked computer. Integrated telephone network system and IVR computer network system. Caregivers dialed in and heard the narrator greet them by name, review the menu of four module options, and got the service they requested. The caregiver heard a digitized human voice that spoke a computer-mediated script. Caregivers responded

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					by touching the designated numbers on their phone. Available modules: (1) Weekly caregiver's conversation (interactive automated system that monitored stress levels and provided information on how to manage patient problems, sent alerts to system manager if stress level increased significantly during 3-week period, monthly health self-assessment, reminders about previous advice and TLC features); (2) personal mailbox (allowed caregivers to anonymously send and receive confidential communications with other caregivers or communicate with a clinical nurse specialist); (3) bulletin board (support group over the phone, similar to a chat group, users could post messages and receive responses from other users); (4) activity-respite conversation (offered the patient an 18-minute personalized, pleasant conversation designed to engage the listener in a safe, comforting, and nondemanding activity). Also included "Ask the expert" option for confidential voicemail access to multidisciplinary paen for advice, referrals, or second opinions.
Family-based Psychoeducation	Joling, 2012[215,216] Fair	Reduce depression and anxiety in cgs, as well as burden and improving QOL	Psychoeducation for caregiver and family members with primary goal to increase family involvment in care and support primary caregiver	UC (for The Netherlands)	6 in-person counseling sessions: one individual prparation session followed by 4 structured meetings that included their relatives and/or friends (family meetins), and one additional individual evaluation session. The first session was aimed to prepare the caregiver for the family meetings and to propose the idea of seeking help from family and friends. The aim of the family meetings was to offer psuch-education, teach problem-solving techniques and mobilize the existing family networks of the patient and primary caregiver in order to improve emotional and instrumental support. After the final family session, an individual session was held to evaluate the caregiver's satisfaction with the intervention program and to start additional support when requested.
	Mittleman, 2008[217] Good	Reduce depression in cg, delay pt nursing home placement, improve pt survival	Individual and family counseling sessions + donepezil	Donepezil + UC	In-person counseling sessions, two individual sessions and 3 sessions that included family members. Counseling on demand by telephone also provided. Donepezil (started at 5 mg and was increased to 10 mg/day unless contraindicated).

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		through improved emotional support and assistance of caregiver by other family members			Resource information, help in an emergency, routine services.
Peer support only	Charlesworth, 2008[218] Fair	improve psychological well-being and QOL of cg	Peer befriending (peer not necessarily experienced in caregiving)	UC (in England)	Contact with a local befriending scheme. Befriending volunteers had the role of providing emotional support for their matched carers through companionship and conversation and being a "listening ear." We also permitted informational support or "signposting" in limited, appropriate circumstances. Usual care as provided in their area by health, social, or voluntary services
	Gallagher-Thompson 2003[171] Fair	In cgs, reduce depressive sx, increase use of positive coping strategies, decrease use of negative coping strategies, and be less bothered by pt behavior	REACH Palo Alto: Enhanced support group	Educational materials + brief supportive phone calls (number NR)	IG2 (Enhanced): Enhanced support group. Patterned after typical caregiver support groups in the community and was developed by using the principles outlined in a manual on support groups published by the Alzheimer's Association. It primarily focused on developing peer support rather than on teaching participants how to care for their own needs. Also given 2 packets of materials.
	Pillemer, 2002[219] Fair	Improve psychological well-being of cg	One-on-one Peer support of current or former cgs	No peer contact	Peer Support Project. Volunteers received training and were paired with caregivers. The emphasis was support that persons in the same life situation can provide to one another without professional intervention. The volunteer training focused on social support as well as a tool kit of exercises and activities to conduct with the caregivers. The activities were designed to help the caregivers openly discuss their situations and to discover ways to obtain better support from other network members.
	Winter, 2006[220] Fair	reduce depression and burden in cgs and enhance a sense of personal gain.	Telesupport group	No support group	Telesupport groups were conducted by trained social workers who used conference-calling technology to link 5 caregivers per group for an hour weekly. The primary goal was to enhance caregiver ability to manage daily stressors by providing emotional support and validation. Faciliators initially focus on developing group cohesion. Caregivers express emotions and share coping strategies, assist eachother in problem-

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Group	Study reference USPSTF quality rating	Primary Aim	Intervention Description	Control group	Detailed Intervention Description
					solving, and share educational resources.
Physical activity counseling	Connell 2009[221] Fair	increase cg PA and decrease perceived burden, depression, and stress	Telephone-based motivational interviewing for PA	Written materials at end of study	Health First video featuring spouse caregives discussing strategies for fitting physical activity into their daily routine. Choice of exercise videos (low impact exercise for those with limited mobility or low impact aerobic dance and movement). Booklet "Pep Up Your Life" distributed by the AARP which contains information on flexibility, strength and balance exercises. Health First workbook that explained each step of the program and included forms for participants to keep track of their weekly goals and progress toward their long-term goals. Two motivational newsletters. Telephone counseling calls to address potential or perceived conflicts with participation.
	Hirano 2011[222] Fair	reduce subjective sense of burden and physical symptoms in older adult caregivers through increased physical activity	Exercise prescription	No exercise intervention	Prescribed regular exercise with moderate intensity (3 metabolic equivalents, or METS) 3 times per week. Carried a pedometer that recorded daily steps and asked to record their daily progress of exercise amount in a journal (same as CG).
	King, 2002[223] Fair	Improve fitness, reduce psychological distress, reduce risk of negative CV outcomes, and improve sleep quality through increased exercise	PA counseling for caregivers	Nutrition education	Provided with an exercise prescription in which exercise intensity was gradually increased over the initial 6-week period to 40-59% of heart rate reserve based on the peak heart rate achieved during symptom-limited treadmill testing. Participants were instructed to engage in at least 4 30- to 40-minute exercise sessions per week of primarily brisk walking, in a home-based format. Participants were encouraged to increase other forms of activity throughout the day, such as leisurely walking and gardening. Telephone contact occurred on a biweekly basis during the first 2 months and then once monthly through 12 months. Calls were used to monitor progress, answer questions, and provide feedback. Participants completed brief daily logs to record physical activity. Health educators utilized behavioral strategies based on social cognitive theory.

Abbreviations: AARP = American Associated of Retired Persons; ACT = Advancing Caregiver Training; AD = Alzheimers Disease; cg = caregiver; CG = control group; COPE = Care of Persons with Dementia in their Environment; CTIS = computer-telephone integration system; d = day; DAISY = Danish Alzheimer Intervention Study; DFCC = Dementia Family Care Coordinator; Educ = education; FCC = Family Care

Coordinator; GP = general practioner; IG = intervention group; METS = metabolic equivalent; min = minutes; m = months; NP = nurse practitioner; OT = Occupational Therapist; PA = physical activity; PCP = Primary Care Physician; PIC = Partners in Caregiving; PIP = Psychoeducation Intervention Program; pt = patient; QOL = quality of life; RAI-HC = resident assessment instrument-home care; rec'd = received; REACH = Research for Enhancing Alzheimer's Caregiver Health; sx = syptoms; tx = treatment; UC = usual care; tng = training; UK = United Kingdom; USPSTF = United States Preventive Services Task Force; wl = waitlist.

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Table 6. Selected Instruments Measuring Caregiver Burden or Stress

Acronym	Instrument		Number of items	Instrument target, range, interpretation
(none)	Behavior upset		17	Caregiver upset related to patient's performance of 8 ADLs and 9 IADLs. Range 0 (no upset) to 4 (extreme upset), summary score is average Higher=worse (more upset)
CBI	Caregiver Burden Inventory		24	Caregiver burden related to time/dependency, development, physical health, emotional health, social relationships of caregivers Range 0-96 ≥36=worse (greater need for respite and other services)
CHS	Caregiving Hassle Scale		41	Degree of stress/upset/hassle associated with patient's symptoms; range 0-123, higher scores indicate greater stress
CNI (aka NPI, Caregiver portion)	Caregiver Neuropsychiatric Inventory		Covers 10 symptom domains (unclear on the number of items)	Caregiver distress related to patient's neuropsychiatric symptoms; range 0-60, higher score associated with worse symptoms After rating the frequency and severity of each symptom domain of the NPI, caregivers were asked to rate the emotional or psychological distress they experienced in relation to that symptom on a 6-point scale: 0 (Not at all distressing), 1 (Minimally distressing), 2 (Mildly distressing), 3 (Moderately distressing), 4 (Severely distressing), and 5 (Very Severely or Extremely distressing). Specific anchoring definitions for each scale item are included to enhance internal consistency and reliability.
CRA	Caregiver Reaction Assessment	Disrupted Time	5	Burden related to disrupted time (range 5-25), financial problems (range 3-15), lack of family support (range 5-25), health problems (range 4-20), and self-esteem (range 7-35) 5-point Likert-type response options, ranging from strongly agree to strongly disagree (1=strongly agree, 5=strongly disagree) Higher=worse (greater burden)
		Financial Problems	3	
		Lack of family support	5	
		Health problems	4	
		Self-esteem	7	
ICS	Impact of Caregiving Scale		unknown	Respondents evaluate burden on a Likert scale arising from 4 domains: emotions, social relationships, family relationships, and physical health. Item responses are summed to obtain scores on each subscale, with higher scores indicating greater burden.
RMBPC	Revised Memory and Behavioral Problems Checklist		24	Degree caregiver is bothered by 24 specific patient behaviors Range for total caregiver bother: 0-96 Range for disruption subscale: 0-32 Interpretation not described; higher=worse (greater bother related to patient behavior) Sometimes average "bother" score is calculated for endorsed behaviors, range 0 (not at all) to 4 (extremely)
RSS	Relative's Stress Scale		15	Caregiver stress; range 0-60, >23=moderate to high burden

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Acronym	Instrument	Number of items	Instrument target, range, interpretation
SCB	Screen for Caregiver Burden	25	Measure subjective and objective burden in caregivers of dementia patients. 25 items for which the caregiver responded with 0=no occurrence of the experience, 1=occurrence of the experience with no distress, 2= occurrence with mild distress, 3= occurrence with moderate distress,4=occurrence with severe distress. For objective burden, each item is scored as 0 (did not occur) or 1 (did occur). For subjective burden, the anchor points are 1 (no occurrence or occurrence with no distress), 2 (mild distress), 3 (moderate distress), 4 (severe distress). For objective burden, scores would range between 0 and 100. For subjective distress, scores would range between 25-100.
SPPIC	Self-Perceived Pressure by Informal Care		Burden; range 0-9, high=worse (greater burden)
Zarit CBI, Zarit CBI-12	Zarit Caregiver Burden Interview	2 versions: 22 items, 12 items	General or overall level of burden related to caregiving Range 0-88 (22-item) 0-48 (12-item) Guideline for 22-item version: 0-21: Little or no burden 21-40: Mild to moderate burden 41-60: Moderate to severe burden 61-88: Severe burden

Abbreviations: ADLs = activities of daily living; IADLs = instrumental activities of daily living; NPI = neuropsychiatric inventory.

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Table 7. Selected Depression and Hopelessness Screening Instruments

Acronym	Instrument	Number of items	Range of score, threshold
BDI-I, -II	Beck Depression Inventory, First Edition	21	0 to 63; minimal depression (0-13), mild depression (14-19), moderate depression (20-28), severe depression (29-63)
BHS	Beck Hopelessness Scale	20	0-30; normal (0-3), mild hopelessness (4-8), moderate hopelessness (9-14), severe hopelessness (> 14)
CES-D	Center for Epidemiologic Studies Depression Scale	20	0 to 60; possible cases of depression (≥ 16)
GDS, GDS-15	Geriatric Depression Scale	30 15	Full GDS: 0-30; normal (0-10), borderline (11-13), increased depressive symptoms, associated with depression (14-30) GDS-15: Range 0-15, interpretation unknown
HRSD	Hamilton Rating Scale for Depression	17	Varies by version, 0 to 54 in commonly used version; normal (0-7), moderate depression (≥ 20)
HADS	Hospital Anxiety and Depression Scale	14 (7 specific to depression)	0 to 21; normal (0-7), probable presence or depression (≥ 11),
MADRS	Montgomery-Asberg Depression Rating Scale	10	0 to 60; higher scores indicate greater depressive severity
PHQ-9	Patient Health Questionnaire 9	9 + 1 non-scored item	0-27; minimal depression (1-4), mild depression (5-9), Moderate depression (10-14), moderately severe depression (15-19); severe depression (20-27)
ZSDS	Zung Self-rating Depression Scale	20	20 to 80; normal (<50), mild depression (50-59), moderate to marked depression (60-69), severe depression (>70)

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Table 8. Selected Instruments Measuring Caregiver Psychological or Physical Well-Being

Outcome	Acronym	Instrument	Number of items	Instrument target, range, interpretation
Physical health	MAI	Multilevel Assessment Inventory	8	Physical health of caregivers; range 8 (very poor health) to 27 (perfect health)
	NA	Single item Self-rated Health	1	Self-rated Health: "Compared to 6 months ago, how would you rate your health in general now?"; range 0 (much better now) to 4 (much worse now)
	NA	Health Deterioration	7	Adverse health effects from caregiving; range and interpretation NR
Stress related to caregiving or patient's illness	PCI	Perceived Change Index	13	Changes in caregiver well-being over the past month
	PAIS	Psychosocial Adjustment to Illness Scale	46	Assess adjustment to relatives' cognitive impairment. Items address satisfaction with medical care; impact on relationships, work, and activities; general psychological distress (e.g., felt nervous, tense or afraid; felt sad, depressed, lost interest in things or felt hopeless) Includes subscale for psychological distress (see PAIS-D below). range NR, higher=worse adjustment
Global emotional distress	GHQ	General Health Questionnaire	12	Psychiatric distress; range 0–36; >15=evidence of distress, >20=suggests severe problems and psychological distress
	PAIS-D	Psychosocial Adjustment to Illness Scale, Psychological Distress subscale	NR	Score not described, assume uses items related to psychological distress (e.g., felt nervous, tense or afraid; felt sad, depressed, lost interest in things or felt hopeless) range NR, higher=worse adjustment
	PSS, PSS-10	Perceived Psychological Stress	14, 10	General appraisal of stress in the past month. 10- and 14-item versions. Interpretation NR, but average PSS-10 score for US adult age 65 and older was 12.0 (year NR)
	NA	Distress measure	NR	Study-created measure of distress, Range and interpretation NR
	PSI	Psychiatric Symptoms Index	14	Psychological distress; range 14–56, higher=more distress
Functioning	SF-36	Short Form Health Survey	36	Variety of physical and mental/emotional functioning and well-being subscales, higher=better functioning.
Quality of life	EuroQOL-5D	EuroQOL	5	Health-related quality of life; range 0–100, high=better quality of life
	PWI-A	Personal Well-being Index for Adults	7	Cross-cultural measure of subjective quality of life; range 0–100; "normal" range 60–70

Abbreviations: NA = not applicable; NR = not reported; US = United States.

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Table 9. Study Characteristics for Exercise Intervention Trials

Study reference USPSTF quality rating	n rand	Location	Mean Age	% Female	Mean Edu (y)	MCI or dementia (type) MMSE (mean)	Diagnostic Criteria	Intervention description (format, type of exercise, other co-interventions)	Frequency and intensity	Duration (mo)	Control group
Baker, 2010[226] Fair	IG: 23 CG: 10	US	69.6	51.7	NR	MCI (amnestic) 27.4	Petersen	Partial guided, aerobic training, first 8 sessions, then 1 session per wk supervised, plus daily logs	4/wk, 45–60 min each	6	Stretching and balance exercises
Lam, 2011[227] Fair	IG: 171 CG: 218	Hong Kong	78	76	3.3	MCI (NR) 24.5	CDR=0.5 or Mayo clinic criteria	Partial guided, Tai Chi, classes for 8 to 12 wks, then monthly refresher class, plus video	30 min/wk to 30 min/day	5	Stretching and toning exercise
Lautenschlager, 2008[228] Fair	IG: 85 CG: 85	Australia	69	51	12.4	MCI (NR) NR	1.5 SDs or lower than the mean CERAD	Self-guided, moderate intensity exercise, 1 guided session then self-directed, plus daily logs	3/wk, 50 min each	18	Educational material about memory loss, stress management, healthful diet, alcohol consumption, and smoking
Nagamatsu, 2012[229] Fair	IG1: 28 IG2: 30 CG: 28	Canada	75	100	% HS: 24.4	MCI (NR) 26.8	Score <26 on MoCA and had SMC	Guided, resistance (IG1) or aerobic (IG2) training	2/wk, 60 min each	6	Stretching, range of motion, balance exercises, and relaxation techniques
Steinberg, 2009[230] Fair	IG: 14 CG: 13	US	75	70	NR	Dementia (AD) 17.7	NINCDS-ADRDA	Self-guided, aerobic, strength, and balance training, plus daily logs	7/wk, min NR	3	Home safety assessment
Suzuki, 2012[231] Fair	IG: 25 CG: 25	Japan	76	46	10.9	MCI (NR) 26.7	Petersen	Multi-component exercise group, supervised by physiotherapists	2/wk, 90 min each	12	Education classes (did not address physical activity)

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Study reference USPSTF quality rating	n rand	Location	Mean Age	% Female	Mean Edu (y)	MCI or dementia (type) MMSE (mean)	Diagnostic Criteria	Intervention description (format, type of exercise, other co-interventions)	Frequency and intensity	Duration (mo)	Control group
Teri, 2008[232] Good	IG: 76 CG: 77	US	78	41	13.0	Dementia (AD) 16.7	NINCDS-ADRDA	Self-guided, aerobic, strength, and balance training, plus intensive caregiver education and skills training	7/wk, 30 min each	18	Routine medical or crisis intervention
Tsai, 2012[233] Fair	IG: 28 CG: 27	US	79	73	14.6	MCI/Dementia (NR) 25.5	MMSE 18-28	Guided, Tai Chi, adapted for elders with knee osteoarthritis and cognitive impairment	3/wk, 20-40 min each	5	Attention control (health education, culture-related activities, social acitvities)
Venturelli, 2010[234] Fair	IG: 15 CG: 15	Italy	84	NR	NR	Dementia (NR) NR	NR	Guided, circuit training	3/wk, 45 min each	3	Physiotherapy (electrostimulations, massage, and passive leg movement on bed) and animation (bingo, music therapy, and patchwork)
Vreugdenhil, 2012[235] Fair	IG: 20 CG: 20	Australia	74	60	10.2	Dementia (AD) 22.0	DSM-IV, NINCDS-ADRDA	At-home exercise and walking program, supervised by caregiver	NR	4	Offered intervention at the study conclusion

Abbreviations: ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; CDR = clinical dementia rating; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CG = control group; DSM = Diagnostic and Statistical Manual of Mental Disorders; edu = education; HS = high school; IG = intervention group; MCI = mild cognitive impairment; min = minutes; MMSE = mini-mental state examination; mo = months; MoCA = Montreal Cognitive Assessment; n = number; NINCDS = National Institute of Neurological and Communicative Diseases; NR = not reported; rand = randomized; SD = standard deviation; SMC = subjective memory complaints; US = United States; wk(s) = week(s); y = year.

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Table 10. Study Characteristics for Cognitive Intervention Trials

Study reference USPSTF quality rating	n rand	Location	Mean Age	% Female	Mean Edu	MCI or dementia (type) MMSE score (mean)	Diagnostic Criteria	Cog Rehab† or Training	Cog Stim	Co-Intervention*	Delivered By	Int Intensity and Duration	Control Group Intervention
Greenaway 2012[236] Fair	IG: 20 CG: 20	US	73	61	16.4	MCI (amnestic) 26.8	Petersen	Yes	--	Memory support system (adaptation to memory loss, including coping strategies)	NR	2x/wk (60m) for 6 wks	No intervention. Given a calendar and encouraged to use it on their own.
Kinsella, 2009[237] Fair	IG: 26 CG: 28	AU	77	57	12.0	MCI (amnestic) 26.4	SMC; objective memory impairment on neuropsych-ological tests of memory; no impairment in ADL	Yes	--	Coping strategies education (exercise)	Clinical neuropsych-ologists and OT	1x/wk (90m) for 5 wks	Delayed intervention
Rapp, 2002[238] Fair	IG: 9 CG: 10	US	74	58	%>12 y: 74	MCI (NR) 27.6	Petersen	Yes	--	Relaxation (breathing)	Clinical geropsych-ologists	1x/wk (120m) for 6 wks	Delayed partial intervention, printed materials only
Troyer, 2008[239] Fair	IG: 27 CG: 27	Canada	75.4	54.2	14.8	MCI (amnestic) 27.9	Petersen	Yes	--	Nutrition Stress mgmt/ relaxation Other services (SW)	Psychologist, clinical psychologist, dietician, geriatric social worker	10 sessions (120m each) over 6 mo	Wait list
Tsolaki 2011 Fair[240]	IG: 122 CG: 79	Greece	68	72	9.2	MCI (NR) 27.9	Petersen	Yes	Yes	Psycho-therapeutic techniques	Psychologists	1x/wk (90m), 60 sessions	Wait list
Buschert 2011[241] Fair	IG: 20 CG: 19	GER	73	51	12.8	Mixed (AD and amnestic MCI) 26.4	DSM-IV, NINCDS-ADRDA (dementia); Petersen (MCI)	Yes	Yes	Reminiscence Psychomotor Recreational	NR	1x/wk (120m) for 20 wks	6 sessions, paper-pencil exercises for self-study
Burgener 2008[242]	IG: 24 CG: 19	US	77	47	15.8	Dementia (NR)	NR	Yes	--	Exercise (Tai-Chi)	Tai-Chi instructors;	3x/wk (180m) for	Wait list, delayed

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Study reference USPSTF quality rating	n rand	Location	Mean Age	% Female	Mean Edu	MCI or dementia (type) MMSE score (mean)	Diagnostic Criteria	Cog Rehab† or Training	Cog Stim	Co-Intervention*	Delivered By	Int Intensity and Duration	Control Group Intervention
Fair						NR				CBT Support groups	social workers	40wks 1x/wk (90m) for 40 wks (CBT alt with support groups)	intervention (20 weeks later)
Cahn-Weiner 2003[243] Fair	IG: 17 CG: 17	US	77	59	12.9	Dementia (AD) 24.7	NINCDS-ADRDA	Yes	--	none	Clinical neuropsych-ologist	1x/wk for 6 wks	Attention control, education on aging and dementia
Chapman 2004[244] Fair+	IG; 26 CG: 28	US	76	54	14.6	Dementia (AD) 20.9	NINCDS-ADRDA	--	Yes	none	Speech-language pathologist and master's level speech-language pathology students	1x/wk (90m) for 8 wks	Information on caregiver education classes and option for wait list
Clare 2010[245] Fair	IG: 23 CG: 22	Wales	78	59	11.2	Dementia (AD) 22.9	NINCDS-ADRDA	Yes†	--	Stress management	OT	1x/wk (60m) for 8 wks	None
Kurz, 2012[246] Fair	IG: 100 CG: 101	Germany	74	44	12.5	Dementia (AD) 25.1	ICD-10	--	--	Caregiver training and support, coping strategies	Behavioral therapists	1x/wk (60m) for 12 wks	Site-specific medical management
Olazaran 2004[247] Fair+	IG: 44 CG: 40	Spain	74	60	% Basic: 54.8	Mixed (AD and MCI) NR	NINCDS-ADRDA (dementia); Flicker (MCI)	Yes	Yes	Reality orientation Psychomotor exercises	NR	2x/wk (420m) for 1 y	Psychosocial support alone
Schwenk 2010[248] Fair	IG: 26 CG: 35	Germany	82	64	11.0	Dementia (NR) 21.4	NINCDS-ADRDA	Yes	--	Dual task training Exercise (resistance and balance)	Trainer	2x/wk (240m) for 12 wks	Attention control, motor placebo group training.

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Study reference USPSTF quality rating	n rand	Location	Mean Age	% Female	Mean Edu	MCI or dementia (type) MMSE score (mean)	Diagnostic Criteria	Cog Rehab† or Training	Cog Stim	Co-Intervention*	Delivered By	Int Intensity and Duration	Control Group Intervention
Requena 2004[109] Fair	IG: 18 CG: 18	Spain	77	71	NR	Dementia (AD) 20.8	NINCDS-ADRDA, DSM-IIIR	--	Yes	Donepezil (factorial design)	NR	5x/wk (225m) for 1 y	None
Quayhagen 1995[249] Fair	NR†	US	74	35	12.6	Dementia (AD) NR	NR	Yes†	Yes	none	NR	6 sessions (60m each) over 12 wks	Wait list

*most or all interventions involved CG or family and basic education.
† At followup, the IGs had 53 total participants and the CG had 25.

Abbreviations: AD = Alzheimers Disease; ADL = activities of daily living; alt = alternative; AU = Australia; CBT = cognitive behavioral therapy; CG = control group; cog = cognitive; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders; ; GER = Germany; IG = intervention group; m = minute; MCI = mild cognitive impairment; mgmt = management; MMSE = Mini-mental state examination; mo = month; n = number; NINCDS- ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NR = not reported; OT = occupational therapist; rand = randomized; rehab = rehabilitation; SMC = subject memory complaints; stim = stimulation; SW = social worker; US = United States; wk(s) = week(s); y = year.

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Table 11. Study Characteristics for Other Behavioral Intervention Trials

Study reference USPSTF quality rating	n randomized	Location	Mean Age	% Female	Mean Edu	MCI or dementia (type) MMSE score (mean)	Diagnostic Criteria	Intervention description	Intervention Intensity and Duration	Delivered By	Control Group
Bellantonio, 2008[250] Fair	IG: 48 CG: 52	US†	82	63	NR	Dementia (NR) 14.8	NR	Multidisciplinary assessments (medical and cognitive evaluations; physical function, gait, and balance; nutritional status; guardianship issues, long-term planning, psychosocial adjustment of the residents and families)	4 assessments; further contacts NR	Geriatrician or geriatrics advanced practice nurse, a physical therapist, a dietitian, and a medical social worker	Medical evaluation conducted by the resident's primary care physician
Richard, 2009[251] Fair	IG: 65 CG: 58	Netherlands	76.5	56.9	% 7-11 y: 61.0	Dementia (AD) 22.3	NINCDS-ADRDA	Vascular care (ASA 38-100 mg, vit B6 50 mg, and folic acid 0.5 mg per day; pravastatin 40 mg (if indicated); antihypertensive therapy (if indicated, starting with reducing salt intake and increasing exercise, followed by a diuretic and, if necessary, addition of a beta-blocker and a calcium antagonist; referral if elevated	Visits every 3 months for 2 y	Neurologist or geriatrician	GPs treated patients according to general guidelines for treatment of vascular risk factors.

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Study reference USPSTF quality rating	n randomized	Location	Mean Age	% Female	Mean Edu	MCI or dementia (type) MMSE score (mean)	Diagnostic Criteria	Intervention description	Intervention Intensity and Duration	Delivered By	Control Group
								glucose; smoking cessation (if indicated); attention to diet and physical activity (if overweight)			
Meeuwsen, 2012[252] Good	IG: 87 CG: 88	Netherlands	78	61	% Low: 35.3	Dementia (NR) 22.7	DSM-IV	Usual care from a memory clinic. The memory clinic provided treatment and care coordination. AChEI and memantine in addition to non-drug interventions	Sessions and time NR; 12 m	Memory clinic staff	Usual care from GP
Nourhashemi, 2010[253] PLASA Fair	IG: 574 CG: 557	France	80	69	NR	Dementia (AD) 19.7	NINCDS-ADRDA	Patients and their caregivers evaluations and consultations (management of any identified problems, knowledge of the disease, functional dependency, progression of cognitive decline, review of drugs, nutritional status, gait disorders and walking capacities, behavioral symptoms, caregivers' psychological and	Consultation 2 times per year, mailed written materials	Physicians	Usual care; intervention materials made available at the end of the study

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Study reference USPSTF quality rating	n randomized	Location	Mean Age	% Female	Mean Edu	MCI or dementia (type) MMSE score (mean)	Diagnostic Criteria	Intervention description	Intervention Intensity and Duration	Delivered By	Control Group
								physical health, and legal questions about the safety of the patient)			
Wolfs, 2008[254] Fair	IG: 23 CG: 10	Netherlands	78	64	NR	Mixed (dementia and MCI) 20.2	NR	Multidisciplinary assessment (results discussed at an interdisciplinary meeting in which a definite diagnosis is made and a treatment plan is formulated; GP is sent a summary of the assessments, the multi-axis diagnosis and recommendations for management)	One time assessment	GP	Usual care
Beer, 2011[255] Beer, 2010[256] Fair	IG: 219 CG: 132	Australia†	85	76	NR	Dementia (NR) 11‡	NR	GP (and clinical and direct care staff) education (topics included: communication with residents and family members, personal care and activities, positive values, behaviors of concern, pain management; dementia, depression, and delirium, effective working between	5 modules for GPs; 27 lessons for care facilities in brief 30 min blocks	NR	No education delivered

Appendix E. Study, Population, and Intervention Characteristics for Key Questions 4 and 5

Study reference USPSTF quality rating	n randomized	Location	Mean Age	% Female	Mean Edu	MCI or dementia (type) MMSE score (mean)	Diagnostic Criteria	Intervention description	Intervention Intensity and Duration	Delivered By	Control Group
								GPs and residential care facilities)			
Menn, 2012[257] Fair	IG1: 109 IG2: 110 CG: 171	Germany	80	68	NR	Dementia (NR) 18.7	NR	GP education on basic information about dementia, anamnesis and physical examination, laboratory diagnostics, and psychometric tests. Training on evidence-based dementia treatment and therapy recommendations. Caregiver support groups.	140 additional min of training versus CG; 10 support meetings for caregivers; 2 y for IG1, 1 yr for IG2	Neurologists, psychiatrists, nurses	GP education on basic information about dementia, anamnesis and physical examination, laboratory diagnostics, and psychometric tests.

† Patients were recruited from assisted living.
‡ Median.

Abbreviations: AD = Alzheimer's Disease; CG = control group; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders; GP = general practitioner; IG = intervention group; n = number; MCI = mild cognitive impairnment; min = minute; MMSE = Mini-mental state examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NR = not reported; PLASA = Plan de Soin et d'Aide dans la maladie d'Alzheimer; y = year;.

Appendix F. Abbreviated Evidence Tables for Key Question 4

Table 1. Cognitive Status Outcomes From AChEI Trials

Medication/ Supplement Class	Study	Specific condition	N randomized	Drug (Dosage)	Measure	Time	Intervention Group	Control Group	p-value	Notes and related outcomes
Donepezil	Doody, 2009[105,106]	MCI	IG: 409 CG: 412	5-10 mg	ADAS-cog, mean (SD)	BL	18.3 (6.6)	18.2 (7.0)	NR	Also report SDMT, PDQ-R, DSB, all NSD between groups at 11m. PDQ was statistically significant between group at 11m (p=0.02).
					ADAS-cog, mean change (SE)	11m	-1.0 (0.4)	-0.13 (0.4)	0.01	
					MMSE, mean (SD)	BL	27.5 (1.9)	27.4 (1.9)	NR	
					MMSE, mean change (SE)	11m	0.1 (0.2)	0.0 (0.2)	NSD	
	Requena, 2004[108,109]	AD	IG: 30 CG: 18	5-10 mg	ADAS-cog, mean (SD)	BL	29.77 (12.52)	26.06 (8.85)	NSD	Also report FAST. Study also included cognitive training arms which are not reported here.
						12m	36.37 (16.21)	35.33 (11.50)	NR	
						24m	38.33 (11.70)	44.72 (13.11)	NR	
					MMSE, mean (SD)	BL	21.17 (7.56)	19.39 (4.92)	NSD	
						12m	17.80 (7.59)	13.11 (5.87)	NR	
						24m	13.87 (7.33)	8.61 (6.70)	NR	
	Raina, 2008	AD	Total: 2275	NR	ADAS-cog, WMD (95% CI)	NR	-2.83 (-3.29, -2.37)	NA	<0.001	Note that this is the WMD, so the results apply to the IG versus the CG.
			Total: 3532	NR	MMSE, WMD (95% CI)	NR	1.14 (0.76, 1.53)	NA	<0.001	
		VaD	1219	NR	ADAS-cog, WMD (95% CI)	NR	-2.16 (-3.00, -1.34)		<0.001	
				NR	MMSE, WMD (95% CI)	NR	1.10 (0.64, -0.15)		<0.001	
		MCI	1060	NR	ADAS-cog, WMD (95% CI)	NR	-0.93 (-2.73, 0.87)		0.31	
Rivastigmine	Ballard, 2008[115] VantagE Study	VaD including probable	IG: 365 CG: 345	3-12 mg	ADAS-cog, mean (SD)	BL	23.0 (9.9)	23.7 (9.8)	NSD	Also report VaDAS scale, difference between groups at 6m was statistically significant (p=0.028).
					ADAS-cog, mean change (SE)	6m	-0.7 (0.38)	0.4 (0.38)	0.029	
					MMSE, mean (SD)	BL	19.2 (4.1)	19.3 (3.9)	NSD	

Appendix F. Abbreviated Evidence Tables for Key Question 4

Medication/ Supplement Class	Study	Specific condition	N randomized	Drug (Dosage)	Measure	Time	Intervention Group	Control Group	p-value	Notes and related outcomes
					MMSE, mean change (SE)	6m	0.4 (0.18)	-0.2 (0.18)	0.007	
	Feldman, 2007[116] Study 304	AD	IG1: 227 IG2: 229 CG: 222	2-12 mg	ADAS-cog, mean (SD)	BL	IG1: 28.1 (12.5) IG2: 27.7 (12.3)	28.5 (12.3)	NSD	Both IG1 and IG2 had significant changes from BL in ADAS-cog; also report ADAS-cogA.
					ADAS-cog, mean change (SD)	6m	IG1: -0.2 (7.3) IG2: 1.2 (7.2)	2.8 (7.2)	IG1: <0.001 IG2: 0.019	
					MMSE, mean (SD)	BL	IG1: 18.4 (4.7) IG2: 18.8 (4.7)	18.6 (4.7)	NSD	Both IG1 and IG2 had significant changes from BL on the MMSE.
					MMSE, mean change (SD)	6m	IG1: 0.3 (3.6) IG2: -0.6 (3.6)	-1.4 (3.6)	NR	
	Mok, 2007[117]	VaD (subcortical)	IG: 20 CG: 20	6 mg	MMSE, mean (SD)	BL	13.0 (4.2)	13.6 (6.0)	NR	Also report FAB total and subscales, all NSD between groups at 6m.
						6m	13.6 (5.8)	13.5 (6.8)	0.563	
	Winblad, 2007[118-127] IDEAL Study	AD including probable	IG1: 293 IG2: 303 IG3: 297 CG: 302	IG1: 9.5 mg/24 hour patch IG2: 17.4 mg/24 hour patch IG3: 12 mg capsule	ADAS-cog, mean (SD)	BL	IG1: 27.0 (10.3) IG2: 27.4 (9.7) IG3: 27.9 (9.4)	28.6 (9.9)	IG1: NSD IG2: NSD IG3: NSD	Also report TMT and 10-point Clock Drawing; only the TMT had a significant difference between groups at 6m.
					ADAS-cog, mean change (SD)	6m	IG1: -0.6 (6.4) IG2: -1.6 (6.5) IG3: -0.6 (6.2)	1.0 (6.8)	IG1: 0.005 IG2: <0.001 IG3: 0.003	
					MMSE, mean (SD)	BL	IG1: 16.7 (3.0) IG2: 16.6 (2.9) IG3: 16.4 (3.0)	16.4 (3.0)	IG1: NSD IG2: NSD IG3: NSD	

Appendix F. Abbreviated Evidence Tables for Key Question 4

Medication/ Supplement Class	Study	Specific condition	N randomized	Drug (Dosage)	Measure	Time	Intervention Group	Control Group	p-value	Notes and related outcomes
					MMSE, mean change (SD)	6m	IG1: 1.1 (3.3) IG2: 0.9 (3.4) IG3: 0.8 (3.2)	0.0 (3.5)	IG1: 0.002 IG2: <0.001 IG3: 0.002	
	Raina, 2008	AD	Total: 1582	NR	ADAS-cog, WMD (95% CI)	NR	-3.91 (-5.48, -2.34)	NA	<0.001	Note that this is the WMD, so applies to the IG versus the CG.
			Total: 1171	NR	MMSE, WMD (95% CI)	NR	-0.04 (-1.28, 1.20)	NA	0.95	
Galantamine	Auchus, 2007[110] GAL-INT-26 Study	VaD	IG: 397 CG: 391	16-24 mg	ADAS-cog/11, mean (SD)	BL	22.9 (9.5)	22.5 (9.5)	NR	
					ADAS-cog/11, mean change (SD)	6m	-1.7 (6.0)	-0.3 (6.4)	0.001	
	Rockwood, 2006[111-114] VISTA	AD	IG: 64 CG: 66	16-24 mg	ADAS-cog, mean (SD)	BL	24.2 (6.4)	27.9 (8.4)	NR	Followup ADAS-cog values estimated from figures, 2m followup also reported.
					ADAS-cog, mean change	4m	-1.8	0.3	0.04	
	Raina, 2008	AD	Total: 4479	NR	ADAS-cog, WMD (95% CI)	NR	-2.46 (-3.47, -1.44)	NA	<0.001	Note that this is the WMD, so applies to the IG versus the CG.
Memantine	Bakchine, 2008[128]	AD (probable)	IG: 318 CG: 152	20 mg	ADAS-cog, mean (SD)	BL	25.9 (10.4)	24.9 (9.7)	NR	Also report difference between groups at each followup time point
					ADAS-cog, mean change	3m	-2.46	-0.7	0.000	
						4m	-2.26	-0.98	0.016	
						6m	-1.93	-1.08	0.156	
	Ferris, 2007[129]	MCI	IG: 30 CG: 30	20 mg	NR	3m	NA	NA	NA	No global cognitive outcome measures. Also report Rey AVLT, NSD between groups at 3m.
	Porsteinsson, 2008[130] MEM-MD-12 Study	AD (probable)	IG: 217 CG: 216	20 mg	ADAS-cog, mean (SD)	BL	27.9 (10.98)	26.8 (9.88)	NSD	NSD between groups for any visit on ADAS-cog (1, 2, 3, 4, and 6m)
						6m	28.5 (12.83)	28.0 (11.94)	0.184	
					MMSE, mean (SD)	BL	16.7 (3.68)	17.0 (3.63)	NR	
						6m	16.5 (5.38)	16.4 (5.08)	0.123	
	Raina, 2008	VaD	Total: 900	NR	ADAS-cog, WMD (95% CI)	NR	-2.21 (-3.27, -1.15)	NA	0.000	Note that this is the WMD, so applies to the IG versus the CG.

Medication/ Supplement Class	Study	Specific condition	N randomized	Drug (Dosage)	Measure	Time	Intervention Group	Control Group	p-value	Notes and related outcomes
					MMSE, WMD (95% CI)	NR	0.45 (-1.02, 1.92)	NA	0.55	

Abbreviations: AD = Alzheimer's disease; ADAS-cog = Alzheimer's Disease Assessment Scale cognitive subscale; AVLT = Auditory Verbal Learning Test; BL = baseline; CG = control group; CI = confidence interval; DSB = Digit Span Backwards test; FAB = frontal assessment battery; FAST = functional assessment staging; IG = intervention group; m = month(s); MCI = mild cognitive impairment; mg = milligram(s); MMSE = Mini-Mental State Examination; N = number; NA = not applicable; NR = not reported; NSD = no significant difference; PDQ = Perceived Deficit Questionnaire; PDQ-R = Perceived Deficit Questionnaire for Relatives; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SE = standard error; TMT = Trail Making Test; VaD = vascular dementia; VaDAS = Vascular Dementia Assessment Scale; WMD = weighted mean difference.

Appendix F. Abbreviated Evidence Tables for Key Question 4

Table 2. Global Function Status Outcomes From AChEI Trials

Medication/ Supplement Class	Study	Specific condition	N randomized	Drug (Dosage)	Measure	Time	Intervention Group	Control Group	p-value	Notes and related outcomes
Donepezil	Doody, 2009[105,106]	MCI	IG: 409 CG: 412	5-10 mg	CGIC-MCI, mean change (SE)	11m	3.9 (0.1)	3.9 (0.1)	NSD	Also report CDR-SB (NSD between groups at 11m) and PGA (p=0.0009 between groups at 11m).
	Requena, 2004[108,109]	AD	IG: 30 CG: 18	5-10 mg	NR	12/24m	NA	NA	NA	No global function assessment reported.
Rivastigmine	Ballard, 2008[115] VantagE Study	VaD including probable	IG: 365 CG: 345	3-12 mg	ADCS-CGIC, mean change (SE)	6m	4.0 (1.31)	4.1 (1.27)	NSD	BL data for ADCS-CGIC NR. Also report GDS, NSD between groups at 6m.
	Feldman, 2007[116] Study 304	AD	IG1: 227 IG2: 229 CG: 222	2-12 mg	CIBIC+, mean change (SD)	6m	IG1: 3.9 (1.3) IG2: 4.1 (1.3)	4.5 (1.3)	IG1: <0.001 IG2: <0.05	Mean change from BL for both IGs also significantly different from CG at 12 and 24m for CIBIC+. Also report GDS, only IG1 is significantly different from CG at 6m (p<0.05).
	Mok, 2007[117]	VaD (subcortical)	IG: 20 CG: 20	6 mg	NR	6m	NA	NA	NA	No global function assessment report.
	Winblad, 2007[118-127] IDEAL Study	AD including probable	IG1: 293 IG2: 303 IG3: 297 CG: 302	IG1: 9.5 mg/24 hour patch IG2: 17.4 mg/24 hour patch IG3: 12 mg capsule	ADCS-CGIC, mean change (SD)	6m	IG1: 3.9 (1.2) IG2: 4.0 (1.3) IG3: 3.9 (1.3)	4.2 (1.3)	IG1: 0.01 IG2: 0.054 IG3: 0.009	BL data for ADCS-CGIC NR. Also report mean change of ADCS-CGIC subscales.
Galantamine	Auchus, 2007[110] GAL-INT-26 Study	VaD	IG: 397 CG: 391	16-24 mg	CIBIC+	6m	NR	NR	NSD	IG showed numerical but not significant improvement on the CIBIC+ than CG (data NR).
	Rockwood, 2006[111-114] VISTA	AD (probable)	IG: 64 CG: 66	16-24 mg	CIBIC+, mean (SD)	BL 4m	3.4 (0.7) 3.7	3.7 (0.9) 4.1	NR 0.03	Followup CIBIC+ values estimated from figures, 2m followup also reported.
Memantine	Bakchine,	AD	IG: 318	20 mg	CIBIC+,	3m	3.90	4.11	0.033	Also report difference

Appendix F. Abbreviated Evidence Tables for Key Question 4

Medication/ Supplement Class	Study	Specific condition	N randomized	Drug (Dosage)	Measure	Time	Intervention Group	Control Group	p-value	Notes and related outcomes
	2008[128]	(probable)	CG: 152		mean change	4m	3.99	4.27	0.012	between group at each followup point
						6m	4.12	4.19	0.523	
	Ferris, 2007[129]	MCI	IG: 30 CG: 30	20 mg	NR	3m	NR	NR	NR	NSD or trends on any of the learning or memory tests of the Psychologix Computerized Test Battery, on the self-report of memory improvement. P-value was < 0.10 on the CogScreen variable at one or more visits.
	Porsteinsson, 2008[130] MEM-MD-12 Study	AD (probable)	IG: 217 CG: 216	20 mg	CIBIC+, mean (SD)	6m	4.38 (1.0)	4.42 (0.96)	0.843	NSD between groups for all visits on the CIBIC+.

Abbreviations: AD = Alzheimer's disease; ADCS-CGIC = Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; BL = baseline; CDR = Clinician Dementia Rating Scale; CDR-SB = Clinical Dementia Rating Scale-Summary of Boxes; CG = control group; CGIC-MCI = Clinical Global Impression of Change-Mild Cognitive Impairment; CIBIC+ = Clinician's Interview-based Impression of Change plus Caregiver Input; GDS = Global Deterioration Scale; IG = intervention group; m = month(s); MCI = mild cognitive impairment; mg = milligram(s); N = number; NR = not reported; NSD = no significant difference; PGA = Patient Global Assessment; SD = standard deviation; SE = standard error; VaD = vascular dementia.

Appendix F. Abbreviated Evidence Tables for Key Question 4

Table 3. Physical Function Status Outcomes From AChEI Trials

Medication/ Supplement Class	Study	Specific Condition	N Randomized	Drug (Dosage)	Measure	Time	Intervention Group	Control Group	P-value	Notes and Related Outcomes
Donepezil	Doody, 2009[105,106]	MCI	IG: 409 CG: 412	5-10 mg	NR	NR	NR	NR	NR	
	Requena, 2004[108,109]	AD	IG: 30 CG: 18	5-10 mg	NR	12/24m	NA	NA	NA	No physical function assessment reported.
Rivastigmine	Ballard, 2008[115] VantagE Study	VaD including probable	IG: 365 CG: 345	3-12 mg	ADCS-ADL, mean (SD)	BL	46.7 (17.7)	46.4 (17.2)	NSD	
					ADCS-ADL, mean change (SE)	6m	-0.1 (0.59)	-0.7 (0.6)	NSD	
	Feldman, 2007[116] Study 304	AD	IG1: 227 IG2: 229 CG: 222	2-12 mg	PDS, mean (SD)	BL	IG1: 49.2 (19.8) IG2: 48.7 (19.5)	49.0 (19.6)	NSD	
					PDS, mean change (SD)	6m	IG1: -1.5 (11.3) IG2: -2.6 (11.1)	-4.9 (11.2)	IG1: <0.001 IG2: <0.05	
	Mok, 2007[117]	VaD (subcortical)	IG: 20 CG: 20	6 mg	Lawton IADL, mean (SD)	BL	2.3 (0.7)	2.3 (0.6)	0.70	
						6m	2.3 (0.5)	2.2 (0.8)	0.299	
	Winblad, 2007[118-127] IDEAL Study	AD including probable	IG1: 293 IG2: 303 IG3: 297 CG: 302	IG1: 9.5 mg/24 hr patch IG2: 17.4 mg/24 hr patch IG3: 12 mg capsule	ADCS-ADL, mean (SD)	BL	IG1: 50.1 (16.3) IG2: 47.6 (15.7) IG3: 49.3 (15.8)	49.2 (16.0)	IG1: NSD IG2: NSD IG3: NSD	
					ADCS-ADL, mean change (SD)	4m	IG1: -0.6 (8.8) IG2: NR IG3: -0.4 (8.1)	-1.6 (9.0)	IG1: NSD IG3: NSD	
						6m	IG1: -0.1 (9.1) IG2: 0.0 (11.6) IG3: -0.5 (9.5)	-2.3 (9.4)	IG1: 0.01 IG2: 0.02 IG3: 0.04	
Galantamine	Auchus, 2007[110] GAL-INT-26 Study	VaD	IG: 397 CG: 391	16-24 mg	ADCS-ADL, mean (SD)	BL	48.3 (17.2)	45.9 (16.8)	NR	
					ADCS-ADL, mean change (SD)	6m	0.8 (9.78)	0.2 (9.12)	0.789	
	Rockwood, 2006[111-114] VISTA	AD (probable)	IG: 64 CG: 66	16-24 mg	DAD, mean (SD)	BL	76.4 (19.7)	70.6 (21.4)	NR	Also report standardized response mean at 4m.
						4m	NR	NR	0.13	

Appendix F. Abbreviated Evidence Tables for Key Question 4

Medication/ Supplement Class	Study	Specific Condition	N Randomized	Drug (Dosage)	Measure	Time	Intervention Group	Control Group	P-value	Notes and Related Outcomes
Memantine	Bakchine, 2008[128]	AD (probable)	IG: 318 CG: 152	20 mg	ADCS-ADL, mean change	3m	-0.67	-0.19	0.480	Also report difference between group for ADCS-ADL.
						6m	-1.99	-2.08	0.912	
	Ferris, 2007[129]	MCI	IG: 30 CG: 30	20 mg	NR	NR	NR	NR	NR	
	Porsteinsson, 2008[130] MEM-MD-12 Study	AD (probable)	IG: 217 CG: 216	20 mg	ADCS-ADL, mean (SD)	BL	54.7 (14.44)	54.8 (13.08)	NSD	NSD between groups for any visit (2, 3, 4m) except at 1m (p=0.01) on the ADCS-ADL.
						6m	51.8 (15.89)	52.0 (15.7)	0.816	

Abbreviations: AD = Alzheimer's Disease; AChEI = acetylcholinesterase inhibitor; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living; BL = baseline; CG = control group; DAD = Disability Assessment for Dementia; GAL-INT-26 = Galantamine International; hr = hour; IADL = Instrumental Activities of Daily Living; IDEAL = Investigation of transDermal Exelon in ALzheimer's disease; IG = intervention group; m: month(s); MCI = mild cognitive impairment; mg = milligram(s); n = number; NA = not applicable; NR = not reported; NSD = no significant difference; PDS = Progressive Deterioration Scale; SD = standard deviation; SE = standard error; VaD = vascular dementia ; VISTA = Video Imaging Synthesis of Treating Alzheimer's disease.

Appendix F. Abbreviated Evidence Tables for Key Question 4

Table 4. Cognitive Status Outcomes From Other Pharmacologic Intervention Trials

Medication/ Supplement Class	Study	N randomized	Drug (Daily Dosage)	Measure	Time	Intervention Group	Control Group	p-value	Notes and related outcomes
Vascular Medications	AD2000 Collaborative Group[133]	IG: 156 CG: 154	Aspirin (75 mg)	MMSE, Median (IQR)	BL	19 (16-22)	19 (15-22)	NSD	Data for 24m and 36m also provided, but the followup was <60%
				MMSE, Mean change	3m	0.3*	0.5*	NR	
					6m	0.5*	0.5*	NR	
					12m	-0.5*	-1.0*	NR	
	Clarke, 2003[141] VITAL Trial	IG: 74 CG: 75	Aspirin (81 mg)	MMSE, ADAS-Cog	3m	NR	NR	NR	MMSE or ADAS-cog scores were not significantly altered by treatment (data NR) 2x2x2 factorial design
	Feldman, 2010[134,135] LEADe study	IG: 314 CG: 326	Atorvastatin (80 mg)	ADAS-Cog, Mean (SD)	BL	22.3 (9.1)	22.5 (9.9)	NSD	Also report MMSE, ADCS-CGIC, modified ADAS-Cog, and CDR
				ADAS-Cog, Mean change (SE)	3m	0.167 (0.269)	0.349 (0.261)	0.6276	
					6m	0.363 (0.341)	0.787 (0.319)	0.3640	
					12m	3.610 (0.449)	4.119 (0.417)	0.4062	
					18m	5.981 (0.557)	6.821 (0.518)	0.2702	
	Sano, 2011[136]	IG: 204 CG: 202	Simvastatin (40 mg)	ADAS-Cog, Mean (SD)	BL	24.5 (9.7)	23.9 (10.5)	0.265	Also report MMSE
				ADAS-Cog, Mean change (SD)	3m	1.89 (5.35)	1.11 (5.32)	NSD	
					6m	2.51 (5.61)	2.32 (5.9)	NSD	
					12m	5.79 (7.76)	5.36 (6.95)	NSD	
					18m	9.51 (9.48)	8.18 (8.7)	NSD	
	Simons, 2002[137]	IG: 24 CG: 20	Simvastatin (80 mg)	ADAS-Cog, Mean (SD)	BL	29.4 (10.4)	4.1 (6.5)	NR	Also report MMSE
				ADAS-Cog, Mean change (SD)	6m	33.2 (11.3)	3.4 (7.0)	NSD	
	Sparks, 2005[138-140] ADCLT trial	IG: 32 CG: 31	Atorvastatin (80 mg)	ADAS-Cog, Mean (SE)	BL	20.6 (1.73)	19.9 (1.73)	0.71	Also report MMSE and CGIC

Appendix F. Abbreviated Evidence Tables for Key Question 4

Medication/ Supplement Class	Study	N randomized	Drug (Daily Dosage)	Measure	Time	Intervention Group	Control Group	p-value	Notes and related outcomes
Gonadal Steroids	Henderson, 2000[146]	IG: 21 CG: 21	Estrogen (1.25 mg)	ADAS-Cog, Mean (SE)	BL	25.1 (2.2)	26.8 (2.8)	NR	
					4m	26.9 (2.6)	27.3 (2.5)	NSD	
	Lu, 2006[147]	IG: 9 CG: 9	Testosterone (75 mg)	ADAS-Cog, Mean (SD)	BL	25.0 (13.2)	25.2 (8.9)	NSD	Also report California Verbal Learning Test, Development of Test of Visual Motor Integration, and Judgment of Line Orientation
					6m	27.4 (8.4)	28.3 (10.3)	0.82	
	Mulnard, 2000[148]	IG: 39 CG: 39	Estrogen (1.25 mg)	MMSE, Mean (SD)	BL	20.8 (4.2)	21.1 (3.3)	NSD	A second IG examined the effect of 0.625 mg q.d. No BL data reported for ADAS-Cog Also report CDRS, Emotional face recognition memory score, New dot test memory score, Letter cancellation attention score
				MMSE, Mean change (SD)	12m	-2.7 (3.9)	-3.1 (4.1)	0.64	
				ADAS-Cog, Mean change (SD)	12m	4.8 (5.4)	3.6 (4.7)	0.32	
	Valen-Sendstad, 2010[149]	IG: 33 CG: 32	Estrogen (1 mg) Progesterone (0.5 mg)	MMSE, Mean (SD)	BL	22.0 (4.3)	21.8 (3.9)	NR	Also report Dementia Rating Scale; Word List Memory learning, recall, and recognition; construction praxis copying and recall; Digit Symbol Coding WISC; TMT-A; Boston Naming Test; and Global Deterioration Scale
					12m	19.9 (4.7)	19.8 (4.9)	0.90	
	Wang, 2000[150]	IG: 25 CG: 25	Estrogen (1.25 mg q.d.)	Cognitive Assessment Screening Instrument (CASI), Mean (SD)	BL	57.5 (15.7)	56.3 (14.6)	0.780	Also report CASI short- and long-term memory and attention
				CASI, Mean change (SD)	3m	1.0 (8.0)	0.5 (8.2)	0.850	

Appendix F. Abbreviated Evidence Tables for Key Question 4

Medication/ Supplement Class	Study	N randomized	Drug (Daily Dosage)	Measure	Time	Intervention Group	Control Group	p-value	Notes and related outcomes
				ADAS-Cog error score, Mean	3m	20.5*	20.7*	NSD	
					6m	18.8*	22.1*	0.003	
					9m	20.8*	22.8*	0.18	
					12m	20.3*	23.6*	0.055	
Vitamins and Supplements	Aisen, 2008[151]	IG: 240 CG: 169	Folic acid (5 mg) Vitamin B12 (1 mg) Vitamin B6 (25 mg)	ADAS-Cog, Mean (SD)	BL	22.43 (9.0)	22.63 (8.6)	p=0.52 for rate of change across groups based on GEE model	Also report MMSE and CDR
				ADAS-Cog, Mean change (SD)	3m	1.58 (5.61)	1.51 (4.68)		
					6m	2.44 (6.04)	1.72 (4.74)		
					12m	4.42 (6.61)	4.46 (6.32)		
					18m	7.38 (9.72)	6.54 (8.17)		
	Clarke, 2003[141] VITAL Trial	IG: 74 CG: 75	Folic acid (2 mg) Vitamin B12 (1 mg)	MMSE and ADAS-Cog	3m	NR	NR	NSD	MMSE and ADAS-Cog scores were not significantly altered by treatment (data NR) 2x2x2 factorial design
	Clarke, 2003[141] VITAL Trial	IG: 75 CG: 74	Vitamin E (500 mg) Vitamin C (200 mg)	MMSE and ADAS-Cog	3m	NR	NR	NSD	MMSE and ADAS-Cog scores were not significantly altered by treatment (data NR) 2x2x2 factorial design
	Connelly, 2008[152]	IG: 30 CG: 27	Folic acid (1 mg)	MMSE, Mean (SD)	BL	23.48 (4.1)	23.5 (2.75)	NR	IG and CG also received an AChEI of the clinician's choice
				MMSE, Mean change (SD)	6m	0.09 (3.3)	0.22 (2.67)	NR	Also report the number of responders with an improvement or no deterioration in MMSE score (p=0.02 between groups)
	Freund-Levi, 2006[154,155]	IG: 103 CG: 101	DHA (430 mg) EPA (150 mg)	ADAS-Cog, Mean (95% CI)	BL	25.7 (23.6, 27.8)	27.2 (25.1, 29.4)	NR	
					6m	27.7 (25.4, 30.0)	28.3 (26.0, 30.6)	NR	
	Kwok, 2011[156]	IG: 70 CG: 70	Methylcobalamin (1 mg)	MMSE, Mean (SD)	BL	16.5 (4.9)	16.6 (4.6)	NR	Also report MDRS
				MMSE,	24m	-2 (-5, 0)	-2 (-5, 0)	0.998	

Medication/ Supplement Class	Study	N randomized	Drug (Daily Dosage)	Measure	Time	Intervention Group	Control Group	p-value	Notes and related outcomes
			Folic acid (5 mg)	Median change (IQR)					
	Sano, 1997[157]	IG: 85 CG: 84	Vitamin E (2,000 IU or 1818 mg)	ADAS-Cog, Mean change	24m	8.3	6.7	NR	Also report MMSE, CDR, and Blessed Dementia Scale
	Quinn, 2010[159]	IG: 238 CG: 164	DHA (2 g)	ADAS-Cog, Mean (SD)	BL	23.77 (8.9)	23.96 (9.2)	NR	Also report CDR, MMSE, and rate of change in ADAS-Cog and CDR
				ADAS-Cog, Mean change (SD)	6m	2.5	3.1	NR	
					12m	3.8*	5.6*	NR	
					18m	8.1*	8.8*	0.41	
	Sun, 2007[160]	IG: 45 CG: 44	Mecobalamin (0.5 mg) Multivitamin†	ADAS-Cog, Mean (SD)	BL	24.0 (12.3)	21.2 (10.5) -	NR	Also report MMSE and CASI
				ADAS-Cog, Mean change (95% CI)	6m	0.67 (-2.33, 3.69)	0.9 (0.277, 0.85)	0.34	
	van Uffelen, 2008[161-163]	IG: 90 CG: 89	Folic acid (5 mg) Vitamin B12 (0.4 mg) Vitamin B6 (50 mg)	MMSE, Mean	BL	28.4	29.0	NR	Also report auditory verbal learning test, stroop color test tasks, digit symbol substitution, and verbal fluency
					6m	28.4	28.0	NR	
					12m	28.4	29.0	NR	
	Yurko-Mauro, 2010[164]	IG: 242 CG: 243	DHA (900 mg)	MMSE, Mean (SD)	BL	28.3 (1.3)	28.2 (1.3)	NR	Also report CANTAB Pair Associate Learning, Verbal Recognition Memory, Pattern Recognition Memory, Stockings of Cambridge Problems Solved, and Spatial Working Memory
					6m	28.0 (1.9)	27.9 (1.9)	0.866	
NSAIDs	Aisen, 2003[143]	IG: 118 CG: 111	Naproxen (440 mg)	ADAS-Cog, Mean (SD)	BL	24.4 (10.2)	24.2 (9.6)	0.92	Also report CDR
					12m	30.2 (13.9)	29.9 (13.7)	0.96	
	de Jong, 2008[144]	IG: 26 CG: 25	Indomethacin (100 mg)	ADAS-Cog, Mean (SD)	BL	20.2 (8.3)	19.7 (8.8)	NSD	Also report ADAS-noncog, MMSE, and CIBIC
				ADAS-Cog, Mean change (SD)	6m	4.8 (5.8)	3.9 (4.5)	NSD	
					12m	7.8 (7.6)	9.3 (10.0)	NSD	

Appendix F. Abbreviated Evidence Tables for Key Question 4

Medication/ Supplement Class	Study	N randomized	Drug (Daily Dosage)	Measure	Time	Intervention Group	Control Group	p-value	Notes and related outcomes
	Pasqualetti, 2009[142]	IG: 66 CG: 66	Ibuprofen (800 mg)	ADAS-Cog, Mean (SD)	BL	26.8 (10.6)	25.6 (10.7)	0.515	Also report MMSE, CDR, and CIBIC
				ADAS-COG, Mean change (SE)	12m	-3.0 (1.3)	-3.1 (1.3)	0.951	
					18m	-6.3 (2.4)	-6.2 (3.0)	NR	
	Soininen, 2007[145]	IG: 285 CG: 140	Celecoxib (400 mg)	ADAS-Cog, Mean (SD)	BL	24.8 (10.7)	24.6 (10.1)	NSD	Also report CIBIC, MMSE, and number of patients experiencing deterioration based on ADAS-Cog
				ADAS-Cog, Mean change (SD)	3m	0.77	0.69	0.897	
					6m	1.64	2.15	0.461	
					12m	4.39	5.00	0.541	

*Estimated from a figure.

† Multivitamin contained folic acid, pyridoxine HCl, ferrous (60 mg), nicotinamide (10 mg), calcium carbonate (250 mg), riboflavin (2 mg), thiamine mononitrate (3 mg), calcium panthothenate (1 mg), ascorbic acid (100 mcg), iodine (100 mcg), copper (150 mcg), vitamin B12 (3 mcg), vitamin A (4,000 IU) and vitamin D3 (400 IU).

Abbreviations: AChEI = acetylcholinesterase inhibitor; ADAS-Cog = Alzheimer's Disease Assesment Scale- cognitive subscale; ADCLT = Alzheimer's Disease Cholesterol-Lowering Treatment; ADCS-CGIC = Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; BL = baseline; CANTAB = Cambridge Neuropsychological Test Automated Battery; CASI = Cognitive Assesment Screening Instrument; CDR = Clinical Dementia Rating; CDRS = Clinical Dementia Rating Scale; CG = control group; CGIC = Clinical Global Impression of Change; CIBIC = Clinician's Interview-Based Imppresion of Change; DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; GEE = Generalized Estimated Equation; IG = intervention group; IQR = Inter-Quartile Range; IU = International unit; ; m = month(s); mg = milligram; MMSE = Mini-mental state examination; NR = not reported; NSAIDs = Non Steroidal Anti-Inflammatory Drug(s); NSD = no significant data; q.d. = one a day; SD- standard deviation; SE = standard error; TMT-A = Trail Making Test-part A; WISC = Wechsler Intelligence Scale for Children.

Appendix F. Abbreviated Evidence Tables for Key Question 4

Table 5. Caregiver Depression Outcomes From Caregiver Intervention Trials

	Study	N Randomized	Measure	Time	Intervention Group	Control Group	P-Value	Notes and Related Outcomes
Group Psychoeducational Programs	Belle 2006[165] REACH II	IG: 323 CG:319	CESD ≥15, n (%)	6m	37 (12.6%)	65 (22.7%)	<0.01	White subgroup showed greatest difference, Black, Hispanic NSD
	Burgio 2003[167] REACH-Birmingham	IG: 70 CG: 70	CESD, mean (SD)	BL	15.7 (9.4)	11.4 (9.9)	0.35	No treatment x race effect (p=0.97)
				6m	13.6 (11.6)	12.1 (9.9)		
	Chu 2011[168]	IG: 43 CG: 42	BDI-II, adjusted mean	BL	9.3	11.4	0.13	GEE estimate (SE):
				3m	5.8	10.5	0.05	-2.7 (1.4)
				4m	5.3	11.0	<0.01	-3.6 (1.4)
	Coon 2003[169]	IG1: 53 IG2: 64 CG: 52	MAACL depression subscale, mean (SD)	BL	IG1:16.4 (1.3) IG2: 17.8 (1.4)	14.6 (1.3)	0.02	Treatment x time effect, combining both IGs vs. CG
				7m	IG1: 15.0 (1.3) IG2: 15.4 (1.3)	16.5 (1.3)		
	de Rotrou, 2011[170]	IG: 79 CG: 78	MADRS, mean (SD)	BL	9.0 (7.5)	10.2 (9.2)	0.42	Group x time p-value=0.373
				3m	8.2 (7.5)	10.1 (9.9)	0.21	
				6m	8.9 (7.8)	11.4 (10.3)	0.14	
	Gallagher-Thompson 2003[171] REACH-Palo-Alto	IG1: NR CG: NR Total n randomized: 257	CESD, mean (SD)	BL	IG1: 18.8 (11.5)	17.1 (13.5)	0.51, across 3 groups	White only; no effect in either White or Hispanic subgroups when run separately
				6m	IG1: 15.2 (10.3)	16.0 (10.4)		
				BL	IG1: 16.7 (12.5)	26.7 (14.8)	0.51, across 3 groups	Hispanic only
				6m	IG1: 14.1 (12.3)	22.9 (14.0)		
	Gallagher-Thompson 2008[172]	IG: 87 CG: 97	CESD, mean (SD)	BL	15.1 (10.5)	13.4 (9.4)	0.048, combining ethnic groups	Non-Hispanic White participants only
				6m	11.9 (9.9)	12.8 (9.6)		
				BL	14.8 (12.5)	15.6 (13.6)		Hispanic participants only
				6m	10.3 (10.0)	12.8 (10.3)		
	Hepburn 2001[174]	IG: 72 CG: 45	CESD, mean (SD), controlling for BL	5m	12.0 (7.7)	16.1 (9.1)	0.04	
	Losada, 2010[177]	IG: 88 CG: 79	CES-D, mean (SD)	BL	19.5 (12.7)	17.6 (12.7)	NR	p=0.03 for mean change at 3m
				3m	14.9 (9.7)	17.0 (12.0)	NR	
	Kurz 2010[176]	IG: 156 CG: 136	MADRS, mean (SD) change from BL	15m	-0.9 (7.6)	-0.1 (7.0)	0.38	

Appendix F. Abbreviated Evidence Tables for Key Question 4

	Study	N Randomized	Measure	Time	Intervention Group	Control Group	P-Value	Notes and Related Outcomes
	Ostwald 1999[178]	IG: 72 CG: 45	CESD Mean (SD)	BL	13.1 (8.2)	14.7 (7.6)	0.15	Treatment x time effect
				3m	17.2 (4.1)	18.0 (4.8)		
				5m	12.6 (7.8)	16.2 (9.2)		
	Waldorff, 2012[180]	IG: 163 CG: 167	GDS, mean (SD)	BL	4.7 (5.2)	4.7 (5.0)	NR	
				6m	5.0 (5.1)	5.4 (5.8)	0.52	
				12m	5.6 (5.5)	4.8 (5.7)	0.23	
			GDS, mean difference in change (95% CI)	6m	-0.39 (-0.72, -0.07)	NA	0.018	
				12m	0.91 (-0.21, 2.03)	NA	0.11	
Individual Psychoeducational Programs	Chang 1999[181]	IG: 46 CG: 41	BSI depression subscale, mean (SD)	BL	0.7 (0.7)	0.7 (0.7)	<0.05	Time x treatment effect
				3m	0.6 (0.7)	1.0 (0.9)		
	Gitlin 2003[186] REACH-Philadelphia	IG: NR CG: NR Total n randomized: 255	CESD, mean (SD)	BL	15.3 (12.2)	14.8 (10.7)	0.987	
				6m	15.2 (11.8)	15.0 (11.2)		
	Gitlin 2008[183]	IG: 30 CG: 30	CESD, mean (SD)	BL	14.6 (11.0)	13.2 (9.6)	0.676	
				4m	13.1 (9.4)	14.3 (10.2)		
	Gitlin 2010[187] ACT	IG" 137 CG: 135	% participants with depression (CESD score > 8)	4m	53.0	67.8	0.02	
	Marriott 2000[193]	IG: 14 CG1: 14 CG2: 14	BDI, mean (SD)	BL	11.5 (9.5)	CG1: 12.0 (7.4) CG2: 9.9 (5.5)	<0.05	Per ANCOVA, controlling for baseline
				9m	7.2 (7.5)	CG1: 11.5 (6.8) CG2: 10.9 (5.6)		
				12m	6.3 (5.7)	CG1: 11.4 (7.1) CG2: 11.1 (6.4)		
	Martin-Cook 2005[195]	IG: 24 CG: 25	GDS, Baseline Mean (SD), Followup adjusted mean (SE)	BL	1.8 (1.6)	3.0 (3.3)	NSD	Time x treatment effect
				4m	1.6 (0.5)	2.7 (0.5)		
	Schoenmakers, 2010[197]	IG: 32 CG: 30	BDI, OR (95% CI)	12m	0.16 (0.03, 0.86)	NA	NR	
	Teri 2005[199]	IG: 47 CG: 48	CESD, mean (SD)	BL	14.8 (9.1)	13.2 (8.5)	0.023	Group differences (95% CI) per GEE analysis -2.3 (-6.0, 0.0)
				6m	12.5 (7.7)	15.8 (10.5)		
			HRDS, mean (SD)	BL	6.9 (4.1)	7.6 (5.0)	0.041	Group differences (95% CI) per GEE analysis -1.2 (-2.4, 0.0)
				6m	6.7 (3.9)	8.5 (5.7)		

Appendix F. Abbreviated Evidence Tables for Key Question 4

	Study	N Randomized	Measure	Time	Intervention Group	Control Group	P-Value	Notes and Related Outcomes
	Voigt-Radloff 2011[200]	IG: 71 CG: 70	CESD, mean (SD)	BL	12.1 (7.7)	11.3 (5.9)	NSD	
				6m	10.0 (7.9)	10.0 (6.9)	NSD	
				12m	14.3 (10.3)	12.9 (7.7)	NSD	
	Williams 2010[201]	IG: 59 CG: 57	CESD, mean (SD)	BL	18.7 (10.6)	14.4 (9.6)		
				3m	12.9 (NR)	14.4 (NR)		
				6m	11.9 (NR)	15.2 (NR)		
	Wright 2001[202]	IG: 68 CG: 25	CESD, mean	BL	13	9.7	0.944	Time x treatment effect
				3m	11.7	7.6		
				6m	11.2	6.8		
				12m	10.6	8.2		
Psychoed + Care/Case Management	Bass 2003[203]	IG: 109 (assumed) CG: 73 (assumed)	CESD, mean (SD)	BL	0.57 (0.4)	0.62 (0.45)		
				12m	0.60 (0.39)	0.76 (0.47)	≤0.05	
	Callahan 2006[204]	IG: 84 CG: 69	PHQ-9 depression, mean (SD)	BL	3.8 (5.1)	4.4 (5.6)	NSD	
				6m	3.6 (5.0)	4.3 (5.1)	NSD	
				12m	3.1 (3.9)	4.6 (5.6)	NSD	
				18m	3.1 (4.5)	5.2 (5.3)	<0.05	
	Fortinsky 2009[207]	IG: 54 CG: 30	CESD score, mean (95% CI)	BL	12.1 (8.9, 15.4)	15.1 (10.8, 19.4)	0.73	
				12m	9.8 (6.2, 13.4)	15.0 (10.5, 19.5)		
	Gitlin 2003[185] REACH Memphis	IG1: 67* IG2: 65* CG: 55*	CESD score, mean (SD)	BL	IG1: 13.1 (9.9) IG2: 11.7 (10.2)	11.3 (6.7)		Used IG2 in meta-analysis
				6m	IG1: 14.4 (9.9) IG2: 11.6 (10.0)	12.1 (7.9)	.244	Adjusted for baseline
	Jansen 2011[208]	IG: 54 CG: 45	CESD, mean	BL	10.6	11.2	p=0.172	Time x group interaction
				6m	11.9	9.7		
				12m	11.2	11.2		
Computer / Teletphone-based Psychoeducation	Brennan 1995[212]	IG: 51 CG: 51	CESD, mean (SD)	BL	21.2 (8.1)	15.6 (10.6)		
				12m	18.9 (11.0)	15.7 (10.5)	0.61	
	Finkel 2007[213]	IG: 23 CG: 23	CESD, adjusted mean	BL	7.16	7.16		
				6m	4.32	6.01	0.099	
	Mahoney 2003[214] REACH Boston	IG: 49 CG: 51	CESD, mean (SD)	BL	13. (11.1)	13.5 (11.0)	0.323	Time x group effect, using all 4 time points
				6m	12.3 (9.1)	14.9 (11.7)	0.258	Adjusted 6m effect
				12m	12.4 (11.5)	13.6 (12.0)		
				18m	12.0 (10.3)	14.5 (11.7)		

Appendix F. Abbreviated Evidence Tables for Key Question 4

	Study	N Randomized	Measure	Time	Intervention Group	Control Group	P-Value	Notes and Related Outcomes
Family information and counseling	Joling 2012[215,216]	IG: 96 CG: 96	CESD, adjusted mean (95% CI)	BL	11.4 (10.1, 12.6)	11.9 (10.6, 13.1)	0.266	Group x time effect Incidence of depressive disorder IRR (95% CI) 1.21 (0.69, 1.38)
				6m	12.4 (11.1,13.8)	13.0 (11.6,14.4)		
				12m	12.9 (11.1,14.7)	14.8 (13.3,16.3)		
	Mittleman 2008[217]	IG: 79 CG: 79	BDI	24m	Model results available for change in depressive symptoms	Model results available for change in depressive symptoms	p=0.047	Group x time effect
Peer support	Charlesworth 2008[218]	IG: 116 CG: 120	HADS depression scale, mean (SD)	BL	6.73 (3.62)	6.96 (3.94)		
				6m	6.03 (3.63)	5.84 (3.96)	NSD	
				15m	6.03 (4.00)	6.71 (4.18)	NSD	
				24m	6.25 (4.12)	6.35 (4.59)	NSD	
	Gallagher-Thompson 2003[171]	IG1: NR CG: NR Total n randomized: 257	CESD, mean (SD)	BL	IG2: 14.6 (11.1)	17.1 (13.5)		White only; no effect in either White or Hispanic subgroups when run separately
				6m	IG2: 13.7 (10.9)	13.7 (10.9)	0.51 (3-way group diffs)	
				BL	IG2: 17.0 (12.4)	26.7 (14.8)		Hispanic only; no effect in either White or Hispanic subgroups when run separately
				6m	IG2: 17.3 (14.5)	22.8 (14.0)	0.51 (3-way group diffs)	
	Pillemer 2002[219]	IG: NR CG: NR Total n randomized: 147	CESD	6m	NR	NR	NSD	
	Winter 2006[220]	IG: 58 CG: 45	CESD, mean (SD)	BL	15.9 (11.1)	14.1 (10.8)	NR	
				6m	18.7 (7.2)	20.2 (7.2)	0.121	
Physical activity counsel-ing	Connell 2009[221]	IG: 86 CG: 71	11-item Iowa short form CESD, mean (SD)	BL	9.4 (2.9)	7.9 (2.8)	NR	
				6m	8.1 (3.0)	8.3 (2.9)	NSD	
				12m	8.5 (2.8)	7.7 (2.7)	NSD	
	Hirano 2011[222]	IG: 18 CG: 18	VAS (mm of a line from 0-100 mm)	BL	18.8 (18.7)	39.8 (28.8)	NR	No change from pre to post in either group. Also report VAS occurrence per month (NSD)
			VAS, mean change (SD)	3m	-3.3 (0.3)	1.1 (4.9)	NR	
	King 2002[223]	IG: 51 CG: 49	BDI, mean (SD)	BL	10.7 (6.5)	13.7 (6.3)	NR	
				12m	7.4 (4.8)	9.4 (7.2)	NSD	

*n analyzed, n randomized was not reported.

Appendix F. Abbreviated Evidence Tables for Key Question 4

Abbreviations: ACT = Advancing Caregiver Training; ANCOVA = Analysis of Covariance; BDI = Beck Depression Inventory; BL = baseline; BSI = Brief Symptom Inventory; CESD = Center for Epidemiologic Studies Depression Scale; CG = control group; CI = confidence interval; diffs = differences; GDS = Global Deterioration Scale; GEE = generalized estimating equation; HADS = Hospital Anxiety and Rating Scale; HRDS = Hasegawa's Rating Scale for Dementia; IG = intervention group; IRR = incidence rate ratio; m = months; mm = millimeter; MAACL = Multiple Affect Adjective Checklist; MADRS = Montgomery-Åsberg Depression Rating Scale; n = number; NR = not reported; NSD = no significant difference; PHQ-9 = Patient Health Questionnaire; REACH = Resources for Enhancing Alzheimer's Caregiver Health; SD = standard deviation; SE = standard error; VAS = visual analogue scale; vs.= versus; x = by.

Appendix F. Abbreviated Evidence Tables for Key Question 4

Table 6. Caregiver Burden Outcomes From Caregiver Intervention Trials

	Study	N Randomized	Measure	Time	Intervention Group	Control Group	P-value	Notes and Related Outcomes
Group Psychoeducational Programs	Belle 2006[165] REACH II	IG: 323 CG: 319	Zarit-CBI, n (%) clinically improved (≥0.5 SD)	6m	27 (32.9%)	30 (34.9%)	NSD	Hispanic only
				6m	31 (32.3%)	25 (29.1%)	NSD	White only
				6m	38 (45.8%)	28 (32.9%)	0.008	Black only
	Burgio 2003[167] REACH-Birmingham	IG: 70 CG: 70	RMBPC, total mean (SD)	BL	19.0 (15.9)	19.9 (15.9)	0.52	Average burden reduced in Black but not White participants @ 6m (p=0.002 for treatment by race interaction)
				6m	13.3 (13.5)	15.2 (15.5)		
	Chu 2011[168]	IG: 43 CG: 42	CBI, adjusted mean	BL	79.8	76.0	0.58	GEE est. (SE):
				3m	75.0	75.0	0.16	-3.8 (2.7)
				4m	77.3	76.2	0.36	-2.7 (3.0)
	de Rotrou, 2011[170]	IG: 79 CG: 78	Zarit CBI, mean (SD)	BL	23.0 (14.2)	24.3 (16.9)	0.61	Group x time p-value=0.657
				3m	22.2 (12.5)	23.6 (17.0)	0.55	
				6m	23.0 (14.6)	26.5 (17.0)	0.25	
	Gallagher-Thompson 2003[171] REACH-Palo-Alto	IG1: NR CG: NR [total among 3 groups n=257]	RMBPC, total mean (SD)	BL	IG1: 19.3 (10.7)	19.2 (14.1)		White only; RMBPC bother score available at 3m
				6m	IG1:15.2 (10.3)	16.0 (10.4)	0.54, across 3 groups	
				BL	IG1:18.2 (14.4)	16.0 (9.2)		Hispanic only; RMBPC bother score available at 3m
				6m	IG1:13.9 (12.4)	15.4 (13.9)	0.73, across 3 groups	
	Gallagher-Thompson 2008[172]	IG: 87 CG: 97	RMBPC, average bother rating, mean (SD)	BL	1.6 (1.0)	1.6 (0.6)	0.007, combining ethnic groups	White only
				6m	1.2 (0.8)	1.6 (0.6)		
				BL	1.3 (1.0)	1.2 (0.9)	0.007, combining ethnic groups	Hispanic only
				6m	1.2 (0.8)	1.2 (0.8)		
	Hebert 1994[173]	IG: 24 CG: 21	Zarit CBI, mean (est. from figure)	BL	36	39	NSD	
				8m	37	36		
			RMBPC, reaction, mean (SD)	BL	1.5	1.4	NSD	
				8m	1.6	1.5		
	Hepburn 2001[174]	IG: 72 CG: 45	Zarit CBI, mean (SD), controlling for BL	5m	53.9 (12.4)	59.4 (5.6)	0.051	
	Hepburn 2005[175]	IG: 151 CG: 64	Zarit CBI, mean (SD/SE)	BL	34.8 (12.5)	32.0 (13.7)	NR	
				6m	36.2 (12.2)	34.9 (14.5)	0.25	

Appendix F. Abbreviated Evidence Tables for Key Question 4

	Study	N Randomized	Measure	Time	Intervention Group	Control Group	P-value	Notes and Related Outcomes
				12m	37.0 (13.9)	36.9 (12.7)	0.21	
	Ostwald 1999[178]	IG: 72 CG: 45	Zarit CBI, mean (SD)	BL	56.2 (13.3)	56.5 (15.9)	0.005	Treatment x time effect
				3m	56.8 (11.8)	55.4 (15.9)		
				5m	54.1 (11.2)	59.8 (15.2)		
			RMBPC, reaction, mean (SD)	BL	6.8 (6.3)	5.2 (5.1)	0.01	Treatment x time effect
				3m	5.0 (5.4)	4.4 (4.2)		
				5m	4.1 (4.4)	5.7 (4.4)		
	Ulstein 2007[179]	IG: 90 CG: 90	RSS, mean (SD)	BL	22.0 (10.3)	23.2 (10.8)		
			RSS, mean change (SD)	4.5m	-0.8 (8.5)	-0.7 (7.6)	NSD	
			RSS, mean change (SD)	12m	-2.4 (10.8)	-1.2 (9.5)	NSD	
Individual Psychoeducational	Gitlin 2001[184]	IG: 100 CG: 102	Average upset with patient behaviors, mean (SD)	BL	0.48 (0.27)	0.29 (0.36)		
				3m	0.25 (0.34)	0.34 (0.37)	0.16	Adjusted mean difference at 3m: -0.06 (95% CI, -0.16 to 0.03)
	Gitlin 2003[186] REACH-Philadelphia	IG: NR CG: NR (total n: 255)	RMBPC, mean (SD)	BL	15.8 (13.8)	13.9 (13.9)	0.122	
				6m	12.4 (11.1)	13.3 (13.9)		
	Gitlin 2008[183]	IG: 30 CG: 30	Zarit CBI, mean (SD)	BL	21.0 (9.0)	21.3 (9.2)		Adjusted mean effect at 4m: 0.75 (95% CI, -3.36 to 4.85)
				4m	20.3 (8.8)	20.6 (10.4)	0.72	
	Gitlin 2010[187] ACT	IG: 137 CG: 135	Zarit CBI, mean (SD)	BL	21.2 (9.5)	22.0 (9.6)		
				4m	19.0 (8.5)	21.0 (9.3)	0.05	
				6m	19.1 (9.0)	21.3 (9.8)	0.04	
	Hebert 2003[190]	IG: 72 CG: 72	Zarit CBI, mean (SD)	BL	42.5 (14.6)	41.4 (15.2)	0.71	
				4m	40.1 (14.8)	41.2 (16.6)	0.39	
			RMBPC Total reaction, mean (SD)	BL	2.0 (0.8)	2.2 (0.7)	0.20	RMBPC disruptive behaviors reaction (p<0.01) at 4m
				4m	1.8 (0.7)	2.1 (0.7)	0.04	
	Martin-Carrasco 2009[194]	IG: 55 CG: 60	Zarit CBI, mean (SD)	BL	62.0 (14.9)	58.4 (15.9)	0.30	
				4m	56.6 (16.4)	58.3 (16.7)	0.60	
				10m	54.0 (15.9)	60.5 (16.6)	0.08	
	Teri 2005[199]	IG: 47 CG: 48	Screen for Caregiver Burden, mean (SD)	BL	24.7 (12.4)	23.4 (12.2)	0.029	Group differences (95% CI) per GEE analysis: -4.2 (-7.6, 0.0)
				6m	21.4 (12.5)	25.8 (13.7)		
	Wright 2001[202]	IG: 68 CG: 25	CHS, Mean (SD NR)	BL	27.5	28.5	0.43	Treatment x time effect
				3m	23.5	34.5		
				6m	24.0	24.0		
				12m	22.0	21.4		

Appendix F. Abbreviated Evidence Tables for Key Question 4

	Study	N Randomized	Measure	Time	Intervention Group	Control Group	P-value	Notes and Related Outcomes
Psychoed + Care/Case Management	Callahan 2006[204]	IG:84 CG: 69	CNI, mean (SD)	BL	4.2 (5.6)	6.5 (10.4)	0.08	
				6m	4.4 (6.4)	5.7 (7.2)	0.92	
				12m	3.5 (5.8)	7.7 (8.7)	0.03	
				18m	4.6 (6.3)	7.4 (9.7)	0.33	
	Chu 2000[205]	IG: 37 CG: 38	Zarit CBI, mean	BL	26.2	26.2	NR	Both groups, p<0.05 versus BL at 6m
				3m	26.0	27.5	NR	
				6m	22.3	33.5	<0.05	
				10m	25.3	30.0	NR	
				14m	28.3	33.9	NR	
				18m	27.1	29.5	NR	
	Fortinsky 2009[207]	IG: 54 CG: 30	Zarit CBI, mean (95% CI)	BL	30.4 (26.3, 34.5)	36.0 (30.7, 41.3)	0.73	Reported p-value for time x group effect
				12m	26.2 (21.8, 30.6)	30.6 (25.0, 36.1)		
	Gitlin 2003[185] REACH Memphis	IG1: 67* IG2: 65* CG: 55*	RMBPC, mean (SD)	BL	IG1: 17.0 (13.2) IG2: 13.9 (13.8)	14.0 (11.9)	NR	Used IG2 in meta-analysis. 6m values control for BL values.
				6m	IG1: 14.1 (1.4) IG2: 11.9 (1.4)	13.7 (1.5)	0.413	
	Jansen 2011[208]	IG: 54 CG: 45	SPPIC, mean	BL	3.9	3.3	0.492	Reported p-value for time x group effect
				6m	3.8	2.7		
				12m	4.2	3.3		
	Lam 2010[209]	IG: 59 CG: 43	Zarit CBI, mean (SD)	BL	33.2 (17.8)	32.3 (15.8)	NR	
			Zarin CBI, median change (quartile)	4m	2.0 (-7.0, 9.5)	1.5 (-7.0, 9.3)	NSD	
				12m	5.0 (-10.5, 12.0)	3.5 (-9.3, 12.3)	NSD	
Assessment and treatment	Logiudice 1999[211]	IG: 25 CG: 25	Zarit CBI, mean (SD)	BL	39.0 (8.7)	42.2 (10.3)		
			Zarit CBI, mean change	6m	0.2	4.2	0.20	
				12m	0.77	3.11	0.40	

Appendix F. Abbreviated Evidence Tables for Key Question 4

	Study	N Randomized	Measure	Time	Intervention Group	Control Group	P-value	Notes and Related Outcomes
Computer / Telephone—based Psychoeducation	Brennan 1995[212]	IG: 51 CG: 51	ICS, Emotional Impact of Caregiving subscale, mean (SD)	BL	11.4 (3.2)	11.6 (2.0)		Also report physical impact of caregiving (p=0.47), relational impact of caregiving (p=0.63), and social impact of caregiving (p=0.56) at 12m
				12m	11.0 (3.4)	10.9 (2.5)	0.65	
	Finkel 2007[213]	IG: 23 CG: 23	RMBPC Total, adjusted mean	BL	15.7	10.4		
				6m	15.7	16.9	0.089	
	Mahoney 2003[214]	IG: 49 CG: 51	RMBPC Total, mean (SD)	BL	14.9 (14.4)	11.1 (10.3)	0.14	Time x group effect, using all 4 time points
				6m	11.5 (9.4)	12.8 (11.2)	0.09	Adjusted 6m effect
				12m	14.1 (11.9)	10.3 (11.1)		
				18m	12.2 (11.0)	12.3 (13.1)		
Family information and counseling	Joling 2012[215,216]	IG: 96 CG: 96	CRA, adjusted mean (95% CI)	BL	NR	NR		Randomization x time interaction for subscales at 12m: disrupted time (p=0.053), financial problems (p=0.202), lack family support (p=0.248), health problems (p=0.418) and self-esteem (p=0.296).
				6m	NR	NR	NR	
				12m	NR	NR	NR	
Peer support	Gallagher-Thompson 2003[171] REACH-Palo-Alto	IG2: NR CG: NR [total n=257]	RMBPC Total, mean (SD)	BL	IG2: 16.7 (13.8)	19.2 (14.1)		White only; no effect in either White or Hispanic subgroups when run separately
				6m	IG2:12.4 (10.6)	16.0 (10.4)	0.54 (3-way group diffs)	
				BL	IG2:18.0 (16.0)	16.0 (9.2)		Hispanic only; no effect in either White or Hispanic subgroups when run separately
				6m	IG2: 14.4 (13.0)	15.4 (13.9)	0.73 (3-way group diffs)	
	Winter 2006[220]	IG: 58 CG: 45	Zarit CBI, mean (SD)	BL	33.7 (14.5)	35.0 (15.1)		
				6m	31.7 (15.2)	31.7 (17.3)	0.49	

Appendix F. Abbreviated Evidence Tables for Key Question 4

	Study	N Randomized	Measure	Time	Intervention Group	Control Group	P-value	Notes and Related Outcomes
Physical activity counseling	Connell 2009[221]	IG: 86 CG: 71	RMBPC Total, mean (SD)	BL	14.7 (11.5)	14.4 (9.1)		
				6m	12.9 (10.9)	13.4 (10.0)	<0.05	
				12m	13.2 (12.8)	13.4 (11.9)	NSD	
	Hirano 2011[222]	IG: NR CG: NR (total n: 36)	Zarit CBI, mean (SD)	BL	32.9 (18.2)	38.5 (19.7)		
			Zarit CBI, mean change (SD)	3m	-5.2 (2.1)	0.07 (0.5)	NR	IG showed reduction over time, CG did not
	King 2002[223]	IG: 51 CG: 49	RMBPC Total, mean (SD)	BL	24.6 (15.4)	25.5 (10.3)		Screen for Caregiver Burden also reported
				12m	23.6 (15.4)	23.0 (12.1)	NSD	

*n analyzed, n randomized was not reported.

Abbreviations: ACT = Advancing Caregiver Training; BL = baseline; CBI = Caregiver Burden Interview; CG = control group; CHS = Caregiving Hassle Scale; CI = confidence interval; CNI = Caregiver Neuropsychiatric Inventory; CRA = Caregiver Reaction Assessment ; diffs = differences; est. = estimate; GEE = generalized estimating equation; ICS = Impact of Caregiving Scale; IG = intervention group; m = months; n = number; NR = not reported; NSD = no significant difference; REACH = Resources for Enhancing Alzheimer's Caregiver Health; RMBPC = The Revised Memory and Behavior Problems Checklist; RSS = relative's stress scale; SD = standard deviation; SE = standard error; SPPIC = Self-Perceived Pressure from Informal Care; x = by.

Appendix F. Abbreviated Evidence Tables for Key Question 4

Table 7. Patient Institutionalization Outcomes From Caregiver Trials

Intervention Type	Study	n Randomized	Measure	Time	Intervention Group	Control Group	P-value	Notes and Related Outcomes
Group Psychoeducational Programs	Belle, 2006[165]	IG: 323 CG: 319	Institutionalized, n (%)	6m	14 (4.3)	23 (7.2)	NSD	
	Brodaty, 1989[166]	IG: 36 CG: 32	Nursing home admissions, n (%)	7.8 yrs	26 (79)	27 (90)	NR	
	de Rotrou, 2011[170]	IG: 79 CG: 78	Institutionalized, n	6m	2	1	NR	
	Hebert, 1994[173]	IG: 24 CG: 21	Institutionalized, n	8m	2	5 (1 patient was institutionalized before baseline assessment)	NR	
	Kurz, 2010[176]	IG: 156 CG: 136	Permanent nursing home institutionalizations, n	15m	34	23	0.25	
	Ulstein, 2007[179]	IG: 90 CG: 90	Admitted to a nursing home, n (%)	12m	10 (11.5)	16 (19.0)	NSD	
Individual Psychoeducational Programs	Hebert, 2003[190]	IG: 72 CG: 72	Institutionalized, n (%)	16 wks	11 (15.3)	13 (18.1)	NR	
	Spijker, 2011[198]	IG: 158 CG: 143	Institutionalization rate, n (%)	12m	47 (52.2)	43 (47.8)	1.00	OR (95% CI): 0.98 (0.54, 1.79)
	Graff, 2006[189]	IG: 68 CG: 67	Institutionalized, n	12 wks	3	2	NR	
	Teri, 2005[199]	IG: 47 CG: 48	Institutionalized, n	6m	1	3	NR	
	Voigt-Radloff, 2011[200]	IG: 71 CG: 70	Admitted to a nursing home, n	12m	0	1	NR	
	Wright, 2001[202]	IG: 68 CG: 25	Institutionalized, n (%)	12m	17 (28)	5 (22)	NR	
Psychoed + Care/Case Management	Callahan, 2006[204]	IG: 84 CG: 69	Cumulative nursing home placement, n	6m	3	1	NR	
				12m	7	2	NR	
				18m	7	5	NR	
	Chu, 2000[205]	IG: 37 CG: 38	Institutionalized, n (%)	18m	4 (12.1)	10 (27.8)	NR	

Appendix F. Abbreviated Evidence Tables for Key Question 4

Intervention Type	Study	n Randomized	Measure	Time	Intervention Group	Control Group	P-value	Notes and Related Outcomes
	Eloniemi-Sulkava 2009[225]	IG: 63 CG: 62	Long-term care, percent (95% CI)	12m	6.6 (2.5, 16.7)	15.2 (8.2, 27.2)	NR	Crude hazard ratio= 0.66 (p=0.28)
				18m	12.0 (5.9, 23.5)	24.4 (15.2, 37.8)	NR	
				24 m	24.2 (14.0, 39.9)	28.3 (18.4, 42.1)	NR	
	Eloniemi-Sulvaka, 2001[206]	IG: 53 CG: 47	Cumulative insitutionalization, n (%)	12m	4 (8)	9 (19)	0.09	
				24m	17 (32)	14 (30)	0.80	
	Lam, 2010[209]	IG: 59 CG: 43	Nursing home admission, n	12m	3	1	NR	
	Fortinsky, 2009[207]	IG: 54 CG: 30	Nursing home admission, n (%)	12m	8 (16)	10 (33)	NR	OR=0.40, p=0.10
Technology-based	Finkel, 2007[213]	IG: 23 CG: 23	Institutionalized, n	6m	3	2	NR	
Family Information and Counseling	Mittleman, 2008[217]	IG: 79 CG: 79	Institutionalized, n	5.4y	35	36	NR	
Peer Support	Charlesworth, 2008[218]	IG: 116 CG: 120	Cumulative institutionalization, n	6m	13	11	NR	
				15m	19	13	NR	
				24m	21	17	NR	
Assessment and Referral	Logiudice, 1999[211]	IG: 25 CG: 25	Residential care (not cumulative), n	6m	0	2	0.15	
				12m	6	1	0.30	

*n analyzed, n randomized was not reported.

Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; m = month; n = number; NR = not reported; NSD = no significant difference; OR = odds ratio; wks = weeks; yrs = years.

Appendix F. Abbreviated Evidence Tables for Key Question 4

Table 8. Cognitive Function Outcomes for Exercise Interventions

Study	N randomized	Measure	Time (months)	Intervention Group	Control Group	p-value	Notes and related outcomes
Baker, 2010[226]	IG: 23 CG: 10	Story Recall; List Learning; Delayed-Match-To-Sample	3m	NR	NR	NSD	
Lam, 2011[227]	IG: 171 CG: 218	ADAS-Cog, Mean (SD*)	BL	12.6 (5.1)	14.1 (5.7)	<0.01	Also report MMSE, Category verbal fluency, delay recall, digit span, visual span, Trail A, Trail B, Subjective complaints, and CDR
			5m	10.7 (5.5)	12.8 (6.1)	NSD	
Lautenschlager, 2008[228]	IG: 85 CG: 85	ADAS-Cog, Mean change (95% CI)	6m	-0.26 (-0.89, 0.54)	1.04 (0.32, 1.82)	0.04 (ANCOVA)	Also report word list recall, digit symbol coding, verbal fluency, and CDR
			12m	-0.55 (-1.15, 0.20)	0.04 (-0.66, 0.64)		
			18m	-0.73 (-1.27, 0.03)	-0.04 (-0.46, 0.88)		
Nagamatsu, 2012[229]	IG: 30 CG: 28	Item memory, mean change (SD)	6m	0.55 (1.25)	0.21 (0.76)	NR	IG for resistance training also included in this study. Also report Stroop CW, Trail Making A and B, digit span, associative memory, and everyday problem solving test
Steinberg, 2009[230]	IG: 14 CG: 13	Hopkins Verbal Learning Test, Beta (SE)	3m	0.82 (0.6)	NA	0.19	Random effects model for repeated measures, controlling for MMSE
Suzuki, 2012[231]	IG: 25 CG: 25	MMSE, mean change (95% CI)	6m	0.32 (-0.96, 1.60)	-1.37 (-2.66, -0.07)	NR	Group x time p-value=0.04
			12m	-0.47 (-1.75, 0.81)	-0.44 (-1.74, 0.86)	NR	
Teri, 2008[258]	IG: 76 CG: 77	NA	NA	NR	NR	NA	No cognitive function data reported
Tsai, 2012[233]	IG: 28 CG: 27	MMSE, Mean (SD)	BL	26.04 (1.92)	24.85 (2.64)	NR	Trend p-value=0.223
		MMSE, mean difference from baseline (95% CI)	5m	1.00 (0.32, 1.68)	0.78 (0.04, 1.52)	NR	

Study	N randomized	Measure	Time (months)	Intervention Group	Control Group	p-value	Notes and related outcomes
		MMSE, Between group difference (95% CI)	5m	1.33 (-0.24, 2.90)	NA	0.096	
Venturelli, 2010[234]	IG: 15 CG: 15	MMSE, Mean (SD)	BL	22.3 (2.1)	22.1 (1.7)		
			3m	23.0 (1.4)	17.5 (2.1)	<0.05	
Vreugdenhil, 2012[235]	IG: 20 CG: 20	MMSE, Mean (SD)	BL	22.9 (5.0)	21.0 (6.3)	NR	
			4m	23.9 (5.0)	19.0 (7.7)	NR	
		MMSE, Mean change (SE)	4m	1.0 (1.4)	-1.6 (0.5)	0.001	Adjusted for age, education, baseline score
		ADAS-cog, Mean (SD)	BL	22.7 (9.7)	26.6 (16.6)	NR	
			4m	18.5 (9.8)	30.6 (17.9)	NR	
		ADAS-cog, Mean change (SE)	4m	-4.9 (1.1)	2.1 (1.4)	0.001	Adjusted for age, education, baseline score

* SD assumed.

Abbreviations: Analysis of Covariance; BL = baseline; CDR = Clinical Dementia Rating Scale; CG = control group; CI = confidence interval; CW = Color and Word Test; IG = intervention group; m = month(s); MMSE = Mini-Mental State Examination; N = number; NA = not applicable; NR = not reported; NSD = no significant data; SD = standard deviation.

Appendix F. Abbreviated Evidence Tables for Key Question 4

Table 9. Cognitive Function Outcomes for Cognitive Interventions (Stimulation and Training)

Study	N randomized	Measure	Time (months)	Intervention Group	Control Group	p-value	Notes and related outcomes
Buschert, 2011[241] (MCI)	IG: 10 CG: 12	ADAS-Cog, Mean (SD)	BL	8.7 (2.9)	9.8 (4.3)	NSD	
			6m	7.3 (3.1)	11.7 (5.6)	NR	
Buschert, 2011[241] (Dementia)	IG; 8 CG: 7	ADAS-Cog, Mean (SD)	BL	12.1 (5.3)	16.4 (4.8)	NSD	
			6m	11.4 (6.0)	16.4 (4.9)	NR	
Cahn-Weiner, 2003[243]	IG: 17 CG: 17	HVLT	BL	12.2 (4.6)	12.1 (4.8)	NR	
			3m	11.1 (3.2)	11.0 (3.9)	NR	
Chapman, 2004[244]	IG: 26 CG: 28	ADAS-Cog, Adjusted mean	BL	21.52	20.20	NR	Also report MMSE and CIBIC
		ADAS-Cog, Mean change (95% CI)	12m	4.89 (2.67, 7.11)	5.62 (3.39, 7.85)	NR	
Clare, 2010[245]	IG: 23 CG: 22	Rivermead Behavioral Memory Test, Mean (SD)	BL	5.59 (4.32)	3.91 (5.16)	NR	Also report results for an attention control
			6m	5.44 (6.16)	4.11 (5.68)	NR	
Kinsella, 2009[237]	IG: 26 CG: 28	Prospective Memory Performance, Mean (SD)	BL	1.35 (1.31)	1.85 (1.53)	NR	Prospective Memory Performance is equivalent to Rivermead Behavioral Memory Test
			4m	2.30 (1.34)	1.90 (1.41)	NSD	
Rapp, 2002[238]	IG: 9 CG: 10	NA	NA	NR	NR	NA	
Schwenk, 2010[248]	IG: 26 CG: 35	Dual task in cognitive performance-serial 3 backward, mean percent (SD)	BL	-23.80 (38.71)	-25.51 (35.66)	NR	Also report serial 2 forward
			3m	-4.23 (36.32)	-24.41 (26.66)	0.222	
Troyer, 2008[239]	IG: 27 CG: 27	NA	NA	NA	NA	NA	No multivariate group-by-time interactions on the immediate (p=0.74) or longer-term (p=0.82) objective memory measures
Tsolaki, 2011[240]	IG: 122 CG: 79	MMSE, Mean (SD)	BL	28.09 (1.59)	27.59 (1.88)	0.061	Also report MoCA
			6m	29.00 (6.18)	27.06 (2.34)	0.000	
Requena, 2004[109]	IG: 18 CG: 18	ADAS-Cog, Mean (SD)	BL	32.50 (18.28)	26.06 (8.85)	NSD	Also report MMSE and FAST
			12m	28.56 (21.02)	35.33 (11.50)	NR	
			24m	30.21 (19.41)	44.72 (13.11)	NR	
Quayhagen, 1995[249]	IG: NR CG: NR	Mattis Dementia Rating Scale, Mean (SD)	BL	109.8 (12.0)	109.2 (11.7)	NR	
			3m	113.1 (11.7)	104.8 (13.9)	NR	
			6m	107.6 (15.1)	96.6 (20.2)	NR	

Appendix F. Abbreviated Evidence Tables for Key Question 4

Study	N randomized	Measure	Time (months)	Intervention Group	Control Group	p-value	Notes and related outcomes
Buschert, 2011[241] (MCI)	IG: 10 CG: 12	ADAS-Cog, Mean (SD)	BL	8.7 (2.9)	9.8 (4.3)	NSD	
			6m	7.3 (3.1)	11.7 (5.6)	NR	
Burgener, 2008[242]	IG: 24 CG: 19	MMSE, Mean (SD)	BL	24.8 (3.5)	22.9 (5.2)	0.17	
			5m	25.2 (3.1)	22.4 (7.6)	0.05	
Olazaran, 2004[247]	IG: 33 CG: 40	ADAS-Cog, Mean (SD)	BL	24.7 (1.5)	25.8 (1.6)	0.629	Also report MMSE
		ADAS-Cog, Mean change	3m	0*	0.5*	NR	
			6m	0*	2*	NR	
			12m	4*	6.5*	NR	

* Estimated from a figure.

Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; BL = baseline; CG = control group; CIBIC = Clinician's Interview-Based Impression of Change; FAST = Reisberg Functional Assesment Staging Scale; HVLT = Hopkins Verbal Learning Test; IG = intervention group; m = month(s); MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assesment; N = number; NA = not applicable; NR = not reported; NSD = no significant data; SD = standard deviation.

Appendix F. Abbreviated Evidence Tables for Key Question 4

Table 10. Cognitive Function Outcomes for Cognitive Interventions (Stimulation and Training)

Study	N randomized	Measure	Time (months)	Intervention Group	Control Group	p-value	Notes and related outcomes
Bellantonio, 2008[250]	IG: 48 CG: 52	NR	NR	NR	NR	NR	No cognitive outcomes reported.
Richard, 2009[251]	IG: 65 CG: 58	MMSE, Mean (SD)	BL	22.3 (3.3)	22.2 (3.6)	NSD	p-value at 24 m for between group difference
			12m	19.7 (5.1)	19.5 (5.2)	NR	
			24m	16.8 (8.1)	17.0 (6.4)	0.65	
Wolfs, 2008[254]	IG: 137 CG: 93	MMSE, Mean (SD)	BL	20.5 (6.0)	19.8 (6.6)	NR	Also report GDS
			6m	18.8 (7.8)	19.2 (17.5)	NSD	
			12m	18.0 (7.7)	17.4 (8.8)	NSD	
Nourhashemi, 2010[253] PLASA	IG: 27 CG: 27	NR	NR	NR	NR	NR	No cognitive outcomes reported.
Beer, 2011[255]	IG1: 99 IG2: 62 IG3: 58 CG: 132	NR	NR	NR	NR	NR	No cognitive outcomes reported.

Abbreviations: BL = baseline; CG = control group; GDS = Geriatric Depression Scale; IG = intervention group; m = months; MMSE = Mini-Mental State Examination; N = number; NR = not reported; NSD = no statistically significant difference; PLASA = Plan de Soin et d'Aide dans la maladie d'Alzheimer; SD = standard deviation.

Appendix F. Abbreviated Evidence Tables for Key Question 4

Table 11. Depression Outcomes for Exercise Interventions

Study	N randomized	Measure	Time (months)	Intervention Group	Control Group	p-value	Notes and related outcomes
Lam, 2011[227]	IG: 171 CG: 218	CSDD, Mean (SD*)	BL	0.9 (1.8)	0.8 (1.8)	0.13	
			5m	0.7 (0.9)	0.6 (0.9)	NSD	
Lautenschlager, 2008[228]	IG: 85 CG: 85	BDI, Mean change (95% CI)	6m	-0.94 (-1.77, -0.12)	-0.75 (-1.62, 0.13)	0.44 (ANCOVA)	
			12m	-0.75 (-1.62, 0.12)	-0.44 (-1.29, 0.40)		
			18m	-0.46 (-1.47, 0.55)	-0.51 (-1.44, 0.42)		
Steinberg, 2009[230]	IG: 14 CG: 13	CSDD, Beta (SE)	3m	1.14 (0.4)	NA	0.01	Random effects model for repeated measures, controlling for MMSE
Teri, 2008[258]	IG: 76 CG: 77	CSDD, Mean (SD)	BL	5.7 (3.9)	5.8 (4.5)	0.10	Longitudinal p-value from BL to end of followup
			3m	5.2 (3.6)	6.2 (3.8)		
			6m	6.4 (3.8)	6.5 (4.4)		
			12m	7.0 (4.5)	7.1 (4.5)		
			18m	6.3 (4.3)	7.5 (5.7)		

* SD assumed.

Abbreviations: ANCOVA = analysis of covariance; BDI = Beck Depression Inventory; BL = baseline; CG = control group; CI = confidence interval; CSDD = Cornell Scale for Depression in Dementia; IG = intervention group; m = months; MMSE = Mini-Mental State Examination; N = number NA = not applicable; NSD = no statistically significant difference; SD = standard deviation; SE = standard error.

Appendix G. Trials Pending Assessment

Table 1. Trials Pending Assessment

Study Reference	Study Name	Location	N	Intervention Description	Relevant Outcomes	2013 Status
Annweiler C, Fantino B, Parot-Schinkel E, Thiery S, Gautier J, Beauchet O. Alzheimer's disease-input of vitamin D with mEmantine essay (AD-IDEA) trial: study protocol for a randomized controlled trial. *Trials* 2011, 12:230. PMID: 22014101. Annweiler C, Beauchet O. Possibility of a new anti-alzheimer's disease pharmaceutical composition combining memantine and vitamin D. Drugs & Aging 2012 Feb 1;29(2):81-91. PMID: 22233455.	AD-IDEA	FRA	120	Vitamin D 100,000 IU every 4 weeks	ADAS-cog, MMSE, Frontal Assessment Battery, TMT part A and B, ADAL, IADL, Timed Up and GO, Five Time Sit-to-Stand	In progress
Barnes DE, Chesney M. Preventing loss of independence through exercise (PLIE) – pilot. San Francisco: University of California San Francisco.	PLIE	US	16	Integrative exercise program	ADCS-ADL, QOL-AD, SF-36, falls, ADAS-cog, adverse effects	In progress
Barnes DE. The Mental Activity and eXercise trial for seniors. San Francisco: University of California San Francisco.	MAX	US	126	(IG1) Aerobic exercise (IG2) Computer-based mental activity training	Cognitive function	Completed June 2011, no publications
Belleville S, Hudon C. Measuring the impact of cognitive and psychosocial interventions in patients with mild cognitive impairment. Montreal: Centre de Recherche de l'Institut Universitair de Geriatrie de Montreal.	NR	CAN	162	(IG1) Cognitive training (IG2) Psychosocial intervention	Memory tests, ADLs, MMQ, GDS, GAI, well-being	In progress
Blumenthal JA. ENLIGHTEN: Exercise and NutritionaL Interventions for cognitive and Cardiovasulare HealTh ENhancement. Durham, NC: Duke University.	ENLIGHTEN	US	160	(IG1) Aerobic exercise (IG2) DASH diet (IG3) Aerobic exercise and DASH diet	Executive function (e.g., Digit symbol, trail making test, Stroop test, etc.)	In progress
Boustani M. Indiana University Dementia Screening Trial (IU-CHOICE). Indianapolis, IN: IU Center for Aging Research, 2011. PMID: None.	IU-CHOICE	US	4000	Memory Impairment Screen (MIS)	HRQL, PHQ, anxiety, health care use, advanced care planning	In progress
Boxer AL. Memantine (10mg BID) for the frontal and temporal subtypes of frontotemporal dementia; [Official title] A prospective, randomized, multi-center, double-blind, 26 week, placebo-controlled trial of memantine (10mg BID) for the frontal and temporal subtypes of frontotemporal dementia. *ClinicalTrials.gov [www.clinicaltrials.gov]*, 2007. PMID: None.	NR	NR	140	Memantine 10mg BID	Neuropsychiatric Inventory; Clinical Global Impression Change (CGIC); MMSE; FAQ; UCSF FTD-Neuropsychological Test Battery	Completed December 2012, no publications

Appendix G. Trials Pending Assessment

Study Reference	Study Name	Location	N	Intervention Description	Relevant Outcomes	2013 Status
Burns J. Dose response study of aerobic exercise in older adults. Kansas: University of Kansas Medical Center Research Institute.	NR	US	100	50%, 100% and 150% aerobic exercise program	Cognitive function, memory tests	In progress
Burns J. Pilot study of aerobic exercise in early Alzheimer's disease. Kansas: University of Kansas Medical Center Research Institute.	NR	US	80	Aerobic exercise	Cognitive function, daily function and behavior	In progress
Carrie I, van Kan GA, Gillette-Guyonnet S, et al. Recruitment strategies for preventive trials. The MAPT study (MultiDomain Alzheimer Preventive Trial). Journal of Nutrition, Health & Aging 2012 Apr;16(4):355-9. PMID: 22499458.	NR	FRA	1680	(IG1) Omega-3 supplementation (IG2) Omega-3 + multi-domain intervention (exercise, cognitive training) (IG3) Multi-domain intervention	Cognitive function	In progress
Carter J. A randomised placebo-controlled trial of polyunsaturated omega-3 fatty acid (PFA), in the treatment of dementia; a pilot study. ISRCTN Register, 2006. PMID: None.	NR	UK	50	Polyunsaturated omega-3 fatty acid (PFA)	Cognition (MMSE); quality of life (QOL-AD); general health (GHQ-12)	In progress
Chipman KA. Making memory better for seniors with mild cognitive impairment. Nova Scotia: Capital District Health Authority.	NR	CAN	40	Cognitive training	Rivermead Behavioral Memory Test, CVLT, MMQ, GDS, MAI, MPI, Zarit Burden	NR
Chodosh J. SCAN memory program evaluation study. Los Angeles: VA Greater Los Angeles Healthcare System.	SMPES	US	500	Dementia care management including assessment, education, counseling, referrals and telephone followup	Healthcare use, BPI, FAQ, HRQOL, caregiver burden and depression	Completed March 2012, no publications
Choi SH. Efficacy study of cognitive intervention in amnestic mild cognitive impairment. South Korea: Inha University.	NR	SKO	279	(IG1) Group-based cognitive training (IG2) Home-based cognitive training	Memory tests (e.g., Stroop recall test), MMSE, CDR-SB, QoL, GDS	In progress

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Study Reference	Study Name	Location	N	Intervention Description	Relevant Outcomes	2013 Status
Cyarto EV, Cox KL, Almeida OP, Flicker L, Ames D, Byrne G, Hill KD, Beer CD, LoGiudice D, Appadurai K, Irish M, Renehan E, Lautenschlager NT. The Fitness for the Ageing Brain Study II (FABS II): Protocol for a randomized controlled clinical trial evaluating the effect of physical activity on cognitive function in patients with Alzheimer's disease. *Trials* 2010; 11:120. PMID: 21143943.	Fitness for the Ageing Brain Study II (FABS II)	AUS	230	3 components: PA program; behavioral intervention package; phone monitoring. Asked to do 150 min/week of moderate PA. Given education material about AD.	Geriatric Depression Scale – 15 item; Cambridge Contextual Reading Test; Alzheimer's disease Assessment Scale – Cognitive Section; Standardized Mini-Mental State Examination; Clinical Dementia Rating Scale; Quality of Life – AD; Neuropsychiatric Inventory; Instrumental Activities of Daily Living; Activities of Daily Living; Short Form-36 version 2 (SF-36v2); Zarit Burden Interview.	In progress
Cyarto EV, Lautenschlager NT, Desmond PM, et al. Protocol for a randomized controlled trial evaluating the effect of physical activity on delaying the progression of white matter changes on MRI in older adults with memory complaints and mild cognitive impairment: The AIBL Active trial. BMC Psychiatry 2012 Oct 11;12(1):167. PMID: 23050829.	NR	AUS	156	Physical activity, Modification of the Fitness for Ageing Brain study intervention	Cognitivtion, physical function, physical activity	In progress
Dartigues JF. Efficacy assessment of three non-pharmacological therapies in Alzheimer's disease. Bordeaux, France: University Hospital Bordeaux.	NR	FRA	800	(IG1) Group-based cognitive training (IG2) Reminiscence therapy (IG3) "Made to measure" program (physician chooses either IG1 or IG2)	ADAS-cog, MADRS, MMSE, behavioral disturbaces	Completed December 2012, no publications
Dartigues JF. Efficacy of care management in Alzheimer patients. Bordeaux, France: University Hospital Bordeaux.	NR	FRA	400	Care management (home visits from social worker and regular telephone followups)	NPI, MMSE, CDS, MADRS, QoL, Zarit burden, institutionalization	Competed December 2011, no publications
Dwolatzky T. Computerized personal interventions for Alzheimer's patients. Israel: Shaare Zedek Medical Center.	NR	ISR	159	(IG1) Reminiscence therapy (personalized computer program); (IG2) Cognitive training	Cognitive function	Completed September 2012, no publications

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Study Reference	Study Name	Location	N	Intervention Description	Relevant Outcomes	2013 Status
Dysken M. A randomized clinical trial of vitamin E and memantine in Alzheimer's disease. Minneapolis, MN: Department of Veteran Affairs.	NR	US, PR	620	(IG1) Vitamin E (IG2) Memantine	ADCS-ADL	Completed September 2012, no publications
Elizabeth C. Evaluation of a psycho-educational group programme for dementia care-givers. National Research Register, 2000.	NR	UK	NR	8 week psycho-educational group program	Beck depression inventory; Beck anxiety inventory; carers burden inventory; short anxiety screening test	In progress
Farb NAS. Cognitive activation therapy for MCI: a randomized control study. Ontario: Rothman Research Institute.	FarbMCI2012	CAN	30	Computer-based cognitive activation training (Luminosity) and mindfulness-based stress reduction	Memory, executive function, well-being	In progress
Floeel A. Effects of dietary interventions on the brain in mild cognitive impairment. Berlin, Germany: Charite University.	NR	GER	330	Omega-2 supplementation	ADAS-cog	Completed December 2012, no publications
Forstmeier S, Maerchke A, Savaskan E, Roth T. Cognitive-behavioral treatment for mild Alzheimer's patients and their caregivers. Germany: University of Zurich.	CBTAC	GER	124	Cognitive behavioral therapy including goal setting, psychoeducation, cognitive restructuring, caregiver training and psychosocial interventions	NPI, B-ADL, SCI, AES, CES-D, STAI, STAXI, SF-12, Zarit CBI, SCI for caregiver	In progress
Gates NJ, Valenzuela M, Sachdez PS, Singh NA, Baune BT, Brodaty H, et al. Study of Mental Activity and Regular Training (SMART) in at risk individuals: a randomized double blind, sham controlled, longitudinal trial. BMC Geriatrics 2011; 11:19. PMID: 21510896.	SMART	AUS	120	Cognitive training and progressive resistance training	ADAS-cog, IADLs, well-being, quality of life, neuropsychological test scores	Methods paper published 2011
Gaugler JE, Mittelman M. Comprehensive support for Alzheimer's disease caregivers. Minneapolis, MN: University of Minnesota Clinical and Translational Science Institute	NR	US	161	Enhanced counseling and support for caregivers	Nursing home/institutional placement, caregiver stress, depression and social support	Completed January 2012, no publications
Gertz H. German adaptation of REACH II. Germany: University of Leipzig.	DeREACH	GER	158	"Resources to Enhance Alzheimer's Caregivers Health – second edition" for caregivers	Zarit CBI, PHQ, SF-12	In progress
Hasselbalch SG. Effect of physical exercise in Alzheimer's patients. Denmark: Rigshospital.	NR	DEN	192	Moderate intensity physical exercise	Symbol digit modalities test, NPI, ADAS-cog	In progress

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Study Reference	Study Name	Location	N	Intervention Description	Relevant Outcomes	2013 Status
Heuser I, Frolich L. Trial of simvastatin in amnestic mild cognitive impairment patients. Berlin: Charity University.	SIMaMCI	GER	640	Simvastatin	ADAS-cog, FCSRT score	In progress
Hill C. Aerobic exercise training in mild cognitive impairment. Dallas, TX: University of Texas Southwestern Medical Center.	NR	US	204	Moderate intensity endurance exercise training	Cognitive function	In progress
Holfhoff V. Effectiveness of home-based occupational therapy for dementia. Germany: Dresden University of Technology.	ERGODEM	GER	200	Home-based occupational therapy	ADAS-ADL, cognitive function, behavioral problems, caregiver burden	Completed January 2011, no publications
Janssen Research and Development. A double-blind, placebo-controlled, 2-year study of galantamine used to treat patients with mild to moderate Alzheimer's disease.	NR	US	2051	Galantamine 8-24 mg/d	MMSE, DAD	In progress
Jenson M. The effect of cognitive function as measured by repeated cognitive measures after 12 weeks treatment with donepezil. AstraZeneca	NR	CAN, PER, POL, SWA	155	Donepezil	ADCS-CGIC, NTB, ADAS-cog, CogState computerized neurological test battery	Completed January 2011, no publications
Kivipelto M, Laatikainen TK, Soininen HS, Tuomilehto J, Strandberg TE, Sulkava R, et al. Finnish geriatric intervention study to prevent cognitive impairment and disability. Finland: National Institute for Health and Welfare.	FINGER	FIN	1200	Lifestyle counseling including guided aerobic exercise and muscle training, cognitive training, nutritional guidance	Neuropsychological test battery, Stroop and Trail Making Tests, ADCS-ADS, RAND-36	In progress
Kolassa I. Sensory-cognitive and physical fitness training in mild cognitive impairment. Germany: University of Konstanz.	NR	GER	100	(IG1) Auditory discrimination training; (IG2) physical fitness	ADAS-cog	Completed June 2012, no publications
Krikorian R. Omega-3 and blueberry supplementation in age-related cognitive decline. Cincinnati, OH: University of Cincinnati.	NR	US	140	Omega-3 fatty acid	Memory tests, GDS, GAI	In progress
Laakkonen ML, Holtta EH, Savikko N, et al. Psychosocial group intervention to enhance self-management skills of people with dementia and their caregivers: study protocol for a randomized controlled trial. Trials 2012;13:133. PMID: 22871107.	NR	FIN	160	Psychosocial intervention	HRQoL (15D and SCQ), depression, cognitiveion, GHQ-12, CES-D, caregiver coping	In progress
Laks J. Physical exercise as an additional treatment for Alzheimer disease. Rio de Janiero: Federal University of Rio de Janiero.	NR	BRA	60	Aerobic exercise	CAMCOG, trail making test, physical function	In progress

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Study Reference	Study Name	Location	N	Intervention Description	Relevant Outcomes	2013 Status
Le Duff F. Physical training and cognitive activity on the mild cognitive impairment patient. Nice, France: Centre Hospitalier Universitaire de Nice.	NR	FRA	36	(IG1) Physical training + cognitive activity (IG2) Physical training alone	Cognitive function	In progress
Liu-Ambrose T, Eng J, Boyd J, Hsiung R, Jacova C, Feldman H, Brasher P, Lee P. PROMOTE: Promotion of the mind through exercise. British Columbia: University of British Columbia.	PROMOTE	CAN	70	Aerobic-based exercise training	ADCS-ADL, ADAS-cog	Completed December 2012, no publications
Luchsinger J, Mittleman M, Mejia M, Silver S, Lucero RJ, Ramierez M, et al. The Northern Manhattan Caregiver Intervention Project: a randomized trial testing the effectiveness of a dementia caregiver intervention in Hispanics in New York City. BMJ Open 2012;2:e001941. PMID: 22983877.	NYUCI	US	160	Caregiver intervention addressing psychosocial and economic stressors	GDS, Zaris Caregiver burden	Methods paper published 2012
Markham C. The talking sense communication programme for dementia carers. United Kingdom: University of Portsmouth.	NR	UK	60	The Talking Sense manual including individualized communication development; addresses caregivers knowledge, skills and behavior	Caregiver HADS, QOL	In progress
Masera F. A trial to support caregivers of patients with dementia in Italy: the UP-TECH project. Italy: Istituot Naxionale di Ricovero e Cura per Anziani.	UP-TECT	ITA	900	(IG1) Case manager providing counseling and telephone followups (UP protocol) (IG2) Case manager providing counseling, telephone followups, and other assistive technologies (UP-TECH)	Caregiver burden inventory, days spent at home by patient, QOL	In progress
Montero-Odasso M, Wells LJ, Borrie MJ, Speechley M. Can cognitive enhancers reduce the risk of fs in older people with mild cognitive impairment? A protocol for a randomised controlled double blind trial. *BMC Neurology* 2009; 9:42. PMID: 19674471.	NR	CAN	140	Rx: 5mg donepezil for 1 mo; Rx: increased to 10mg donepezil (per standard treatment)	Attention measured w/ the Digit Span Test; Executive function using the Trail Making Test, parts A & B; Reduction of number falls: The total number of falls by mo. 6 (T2) & proportion of participants who fall are also secondary outcome measures to be evaluated.	In progress

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Study Reference	Study Name	Location	N	Intervention Description	Relevant Outcomes	2013 Status
Nichols LO. Testing the effectiveness of telephone support for dementia caregivers. Memphis, TN: Department of Veterans Affairs.	CONNECT	US	154	Telephone support over the course of year	General well-being and caregivers level of distress	In progress
Orrell M, Yates LA, Burns A, et al. Individual Cognitive Stimulation Therapy for dementia (iCST): study protocol for a randomized controlled trial. Trials 2012 Sep 22;13(1):172. PMID: 22998983.	NR	UK	306	Individual cognitive stimulation therapy	ADAS-cog, QoL-AD, SF-12 for caregiver quality of life	In progress
Pandita-Gunawardena D. An audit to examine the effectiveness of information and counselling strategies in relieving caregiver stress in caregivers of patients with dementia. ISRCTN Register, 2005. PMID: None	NR	UK	100	Enhanced carer counselling	Zait Burden interview	In progress
Pitkala KH, Raivio MM, Laakkonen ML, Tilvis RS, Kautiainen H, Strandberg TE. Exercise rehabilitation on home-dwelling patients with Alzheimer's disease--a randomized, controlled trial. Study protocol. *Trials* 2010; 11:92. PMID: 20925948.	NR	SWE	210	Intervention 1: Home-based physical exercise/rehab. Intervention 2: Day rehab centre-based physical exercise/rehab.	CDR; MMSE; Verbal flow, clock drawing test; FIM; NPI; Cornell depression scale; Falls & fractures; Use of health & social services, admission to permanent institutional care, mortality; Zarit burden scale; GDS; RAND-36; QOL	In progress
Pond CD, Brodaty H, Stocks NP, et al. Ageing in general practice (AGP) trial: a cluster randomised trial to examine the effectiveness of peer education on GP diagnostic assessment and management of dementia. BMC Family Practice 2012;13:12.	AGP	AUS	200 patients, 160 GPs	Two education sessions from GP or nurse providing information about dementia and individualized feedback	GPCOG, CAMCOG, MMSE, GDS, WHOQOL-BREF, BDI, GPAQ, ADL	In progress

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Study Reference	Study Name	Location	N	Intervention Description	Relevant Outcomes	2013 Status
Pot AM. [Public title] Effectiveness of an e-Mental Health intervention for family caregivers of people with dementia; [Official/Scientific title] Effectiveness of an eHealth intervention on psychological well-being, feelings of burden and perceived health of family caregivers of people with dementia. WHO Portal/ICTRP [http://apps.who.int/trialsearch], 2009. PMID: None.	NR	NETH	150	e-Mental Health intervention, called 'Dementie de Baas' ('Mastery over Dementia'). The intervention cosist of 8 lessons & a booster session (follow-up). Working principles are psycho education, cognitive behavioral therapy, problem solving behavior, assertiveness training & relaxation therapy. Participants are in contact w/ a professional counselor (digital coach) who gives them feedback.	Depressive symptoms(CES-D); anxiety(HADS); caregiver stress (RPBMC); feelings of burden (SPICC);subjective health; quality of life; use of care services	In progress
Prick AE. [Public title] Effect of a training program on dementia and caregiving; [Scientific title] A training program for people with dementia and their family caregivers: a randomized controlled trial. Netherlands Trial Register [www.trialregsiter.nl], 2009. PMID: None. Prick AE, de LJ, Scherder E, et al. Home-based exercise and support programme for people with dementia and their caregivers: study protocol of a randomised controlled trial. BMC Public Health 2011;11:894. PMID: 22117691.	NR	NETH	312 (156 dyads)	The goal of the exercise training program is that people with dementia will exercise actively during at least 30 minutes a day. The exercises will include balance, strength training, aerobic/endurance activities & flexibility training. In addition the caregiver will learn how to cope w/ the demented person, will be advised in dementia & the consequences & pleasure activities w/ the patient will be stimulated.	People w/ dementia: Physical health (SIP & SF36); Cognition (neuropsychological research) Caregivers: Physical health (GHQ-12); mood (CES-D); stress (RMBPC & cortisol)	In progress
Rigaud AS. Web-based psycho-educational program to support carers in Alzheimer's patients. Paris: Hospital Broca la Collegiale Memory Clinic.	DIAPASON	FRA	80	Web-based psycho-educational program, lifestyle counseling	Caregiver stress, Zarit CBI, BDI, RCSE	In progress

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Study Reference	Study Name	Location	N	Intervention Description	Relevant Outcomes	2013 Status
Rovner BW, Casten RJ, Hegel MT, Leiby BE. Preventing cognitive decline in older African Americans with mild cognitive impairment: design and methods of a randomized controlled trial. Comt Clin Trials 2012; 33:712-20. PMID: 22406101.	NR	US	200	Manual-based behavioral treatment including goal-setting, activity scheduling, task assignments, identifying avoidant behaviors and rating accomplishments	Episodic member, ADAS neuropsychology tests	Methods paper published 2012
Sadavoy J. Screening for mental health concerns for at-risk community living Chinese seniors. Canada: Mount Sinai Hospital, 2007. PMID: None.	NR	CAN	100	Participants screened for depression and cognitive impairment; only half receive screening results	Health care planning	Not yet recruiting
Saxton J. Cognitive assessment of elderly primary care patients. Pittsburgh, PA: University of Pittsburgh, 2011. PMID: None.	NR	US	524	Patient screened for cognitive impairment; only half of physician received results	Health care planning, cognitive outcomes	Completed August 2012, no publications
Shinto L. Lipoic acid and omega-3 fatty acids for Alzheimer's disease. Portland, OR: Oregon Health and Science University.	NR	US	100	Omega-3 fatty acids	ADAS-cog, ADL	In progress
Sicari R, Berardi N. Train the brain – cognitive and physical training for slowing dementia. Italy: Institute of Clinical Physiology, National Research Council.	Train the Brain (TTB)	ITA	160	Physical activity (aerobics, muscle training, balance, flexibility) and cognitive training	Cognitive function	In progress
Thyrian JR. Intervention study to improve life and care for people with dementia and their caregivers in primary care. Germany: German Center for Neurodegenerative Diseases.	DelpHi	GER	1000	Home visits by Dementia Care Manager to provide care management, counseling and support caregivers	QoL-AD, BIZA-D, NPI, BSI, PHS	In progress
van den Dungen P, Moll van Charante EP, van Marwijk HW, et al. Case-finding of dementia in general practice and effects of subsequent collaborative care; design of a cluster RCT. BMC Public Health 2012;12:609. PMID: 22863299.	NR	NETH	162	Case finding and collaborative care	QoL-AD, EQ5D, MH5, GHQ-12, SSCQ	In progress

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Study Reference	Study Name	Location	N	Intervention Description	Relevant Outcomes	2013 Status
Volkers KM, Scherder EJ. The effect of regular walks on various health aspects in older people with dementia: Protocol of a randomized-controlled trial. *BMC Geriatrics* 2011; 11:38. PMID: 21827648.	NR	NETH	175	Daily 30 minute walk, 5 times a week under supervision.	MMSE Eight words test; Rule shift cards; Key search; Digit span (forward & backward); Face recognition; Picture recognition; Category fluency test; Visual memory span (forward & backward); Picture completion; Stroop task; GDS; QoL - Qualidem; Katz index	In progress
Whitlatch CJ, Judge K, Zarit SH, Femia E. Dyadic Intervention for Family Caregivers and Care Receivers in Early-Stage Dementia. The Gerontologist 2006; 46(5):688-694. PMID: 17050761.	Early Diagnosis Dyadic Intervention (EDDI)	US	34 dyads	9 sessions Objectives: Increase understanding of care preferences/ values of ea. dyad member; discuss/ practice effective communication; discuss discrepancies in care preferences/ expectations; increase dyad's knowledge of available services; explore emotional significance/ relationship issues brought on by the illness for both care partners.	NR	In progress, Baseline

Abbreviations: AD = Alzheimer's disease, ADAS-CGIC = Alzheimer's Disease Assesment Scale-Clinical Global Impression of Change; ADAS-Cog = Alzheimer's Disease Assesment Scale-Cognitive subscale; ADCS-ADS = Alzheimer's Disease Cooperative Study-AIDS Dementia Complex; ADL = activites of daily living; AES = Apathy Evaluation Scale; AUS = Austrailia; B-ADL = Bayer-Activities of Daily Living Scale; BID = twice daily; BIZA = Berlin Inventory of Caregivers' Burden with Dementia Patients; BPI = Brief Pain Inventory; BRA = Brazil; BSI = British Standards Institute; CAMCOG = Cambridge Cognitive Examination; CAN = Canada; CDR-SB = Clinical Dementia Rating-Sum of Boxes; CES-D = Center for Epidemiologic Studies-Depression scale; CGIC = Clinical Global Impression of Change; CVLT = California Verbal Learning Test; DAD = Disability Assesment for Dementia; DASH = Division of Adolescent and School Health; DEN = Denmark; EQ5D = European Quality of Life-5 Dimensions; FAQ = frequently asked questions; FIN = Finland, FIM = Functional Independence Measure; FRA = France; FTD = Frontotemporal Dementia; GAF = Global Assesment of Functioning; GDS = Geriatric Depression Scale; GER = Germany; GHQ-12 = 12-item General Health Questionnaire; GP(s) = general practitioner(s); GPAQ = General Practitioner Alzheimer Questionnaire; HADS = Hospital Anxiety and Depression Scale; IADL = instrumental activities of daily living; IG = intervention group; IN = Indiana; ISR = Israel; ITA = Italy; MADRS = Montgomery-Asberg Depression Rating Scale; MAI = Multilevel Assesment Inventory; MHS = mental health specialist; MIS = Memory Impairment Screen; MMQ = Multifactorial Memory Questionnaire; MMSE = Mini-Mental State Examination; MPI = Multidimensional Prognostic Index; mo = month; N = number; NETH = Netherlands; NPI = Neuropsychiatric Inventory; NR = not reported; NTVB = Neuropsychological Test Battery; PA = physical activity; PER = Peru; PHQ = Patient Health Questionnaire; PHS = public health services; PMID = PubMed Identifier; POL = Poland, PR = Puerto Rico; QOL = quality of life; QOL-AD = Quality of Life-Alzheimer's Disease; RAND-36 = RAND-36 measure of Health-Related Quality of Life; RCSE = Revised scale for Caregiving Self-Efficacy; RMBPC = Revised Memory & Behavior Problem Checklist; Rx = prescription;

SAF = South Africa; SCI = subjective cognitive impact; SCQ = Social Communication Questionnaire; SF-12 = Medical Outcomes Study 12-Item Short Form Health Survey; SF-36(v2) = Medical Outcomes Study 36-Item Short Form Health Survey (version 2); SIP = Sickness Impact Profile; SKO = South Korea; SSCQ = Short Sense of Competence Questionnaire; STAI = State-Trait Anxiety Inventory; STAXI = State-Trait Anger Expression Inventory; SWE = Sweden; TMT = Trail Making Test; T2 = timepoint 2; UK = United Kingdom; WHOQOL-BREF = World Health Organization Quality of Life Assessment-abbreviated.

Appendix H. References Used in Appendixes

1. Lonie JA, Tierney KM, Ebmeier KP. Screening for mild cognitive impairment: a systematic review. Int J Geriatr Psychiatry 2009 Sep;24(9):902-15. PMID: 19226524.
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