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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 in updating its 2014 recommendation on screening for cognitive impairment in older adults. Our review addressed the direct evidence on the benefits and harms of screening for cognitive impairment versus no screening, the test accuracy of screening instruments to detect mild cognitive impairment and dementia, and the benefits and harms of treatment for MCI and mild-to-moderate dementia among community-dwelling older adults ages 65 and older.

Data Sources: We performed an updated search of MEDLINE, PubMed Publisher-Supplied, PsycINFO, and the Cochrane Central Register of Controlled Trials for studies published through January 2019. We supplemented searches by examining reference lists from related articles and expert recommendations and searched federal and international trial registries for ongoing trials.

Study Selection: Two researchers reviewed 11,644 titles and abstracts and 966 full-text articles against prespecified inclusion criteria. We included test accuracy studies that included 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 compared with a reference standard. We included trials of major pharmacologic and nonpharmacologic interventions in people with MCI or mild to moderate dementia and large, observational studies examining adverse effects of these interventions. We conducted dual, independent critical appraisal of all provisionally included studies and abstracted all important study details and results from all studies rated fair or good quality. Data were abstracted by one reviewer and confirmed by another.

Data Analysis: We synthesized data separately for each key question and within sub-categories of screening instruments and treatments. For diagnostic accuracy studies, we focused on sensitivity and specificity of instruments that were evaluated in more than one study. 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 on global cognitive outcomes, global function, and harms; nonpharmacologic interventions aimed at the patient on global cognitive outcomes; and caregiver and caregiver-patient dyad interventions on caregiver burden and depression outcomes. We ran random effects meta-analyses using the DerSimonian and Laird method and sensitivity analyses using a Restricted Likelihood Estimation Model with the Knapp-Hartung correction to calculate the pooled differences in mean changes (for continuous data) and pooled risk ratio (for binary data). We used meta-regression to explore potential effect modification by various study, population, and intervention characteristics in cases where 10 or more studies were pooled. We generated funnel plots and conducted tests for small-study effects for all pooled analyses. Using established methods, we assessed the strength of evidence for each question.

Results: *Screening (Key Questions 1–3):* No published trials examined the direct effect of screening for cognitive impairment on important patient outcomes, including patient, caregiver, and clinician decision-making outcomes or harms. We identified 59 studies that addressed the

diagnostic accuracy of 49 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, a brief test taking 7-10 minutes to complete, remains the most thoroughly studied instrument. The pooled estimate across 15 studies (n=12,796) resulted in 89 percent sensitivity (95% CI, 0.85 to 0.92) and 89 percent specificity (95% CI, 0.85 to 0.93) to detect dementia as a cutoff of ≤23 or ≤24. Other screening instruments evaluated in more than one study included the very brief instruments (≤5 minutes) of the CDT, MIS, MSQ, Mini-Cog, Lawton IADL, VF, AD8, and FAQ and the brief instruments (6 to 10 minutes) of the 7MS, AMT, MoCA, SLUMS, TICS with sensitivity to detect dementia usually at 0.75 or higher and specificity at 0.80 or higher for all instruments. For self-administered, longer tests (>10 minutes), only the IQCODE was assessed in more than one study, with sensitivity to detect dementia ranging from 0.80 to 0.88 and specificity ranging from 0.51 to 0.91. Across all instruments, test performance was generally higher in the detection of dementia versus mild cognitive impairment, although confidence intervals overlapped. No studies directly addressed the adverse psychological effects of screening or adverse effects from false-positive or false-negative testing.

Treatment (Key Questions 4–5): We identified 224 trials and 3 observational studies representing over 240,000 patients and/or caregivers that addressed the treatment or management of MCI or mild to moderate dementia. None of the treatment trials were linked with a screening program; in all cases, trial participants were persons with known mild cognitive impairment (MCI) or dementia.

Pharmacologic Interventions: Based on 45 trials (n=22,431) and 3 observational studies (n=190,076) that evaluated AChEIs (i.e., donepezil, galantamine, rivastigmine) and memantine, these medications may improve measures of global cognitive function in the short term, but the magnitude of change is small. In meta-analyses, the differences in changes between those on AChEIs or memantine compared with those on placebo ranged from approximately 1 to 2.5 points on the ADAS-Cog-11 and 0.5 to 1 point on the MMSE over 3 months to 3 years of followup. AChEIs and memantine appeared to increase the likelihood of improving or maintaining patients' global function by 15 percent (for memantine) to 50 percent (for rivastigmine) in the short term (pooled 95% CI range, 0.49 to 2.69). Other outcome measures were inconsistently reported. Total adverse events and discontinuation due to AEs were more common with AChEIs, but not memantine, compared with placebo. Rates of serious adverse events overall were not higher among those taking medications versus placebo, but individual studies noted increased rates of serious adverse events. Trials evaluating other medications or dietary supplements (k=29; n=6,489), including discontinuing antihypertensives, HMG-CoA reductase inhibitors (atorvastatin and simvastatin), NSAIDs (ibuprofen, naproxen, indomethacin, and celecoxib), gonadal steroids (estrogen [plus or minus progesterone] and testosterone), and dietary supplements and vitamins (multivitamins, B vitamins, vitamin E, 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 61 trials (n=7,847) that evaluated nonpharmacologic patient-level interventions, including cognitive-focused, exercise, and multicomponent and other interventions. Among all interventions, there was no clear benefit on

global or domain-specific measures of cognitive function compared with control conditions at 3 months to 2 years followup. Effect estimates generally favored the intervention groups over control groups, but the magnitude of effect was inconsistent across trials and represented very wide CIs (ranging from no effect to a large effect). Physical function outcomes, including change in ADLs and IADLs, as well as QOL and mental and neuropsychiatric symptoms, were inconsistently reported. There was, however, a pattern of effect for exercise interventions, with small improvements seen in measures of physical function and symptoms for intervention groups, whereas control groups reported worsening function. Caregiver and caregiver-patient dyad interventions including psychoeducation for the caregiver and care and case management interventions, reported in 88 trials (n=14,880), resulted in a consistent benefit on caregiver burden and depression outcomes. Effect sizes were mostly small, however, and were of unclear clinical significance. Little harm was evident in the few nonpharmacologic intervention trials that reported harms.

Limitations: There is a lack of evidence around how screening for and treating MCI and early-stage dementia impacts decision-making outcomes. Furthermore, there has been little reproducibility in testing specific screening instruments in primary care populations. The treatment literature is limited by a lack of consistency in the specific outcomes reported and short followup duration. It is difficult to interpret the clinical importance of the small average effects seen among treatment trials, and many measures likely have limited responsiveness for patients with less pronounced cognitive impairment. Consistent and standardized reporting of results according to meaningful thresholds of clinical significance would be helpful in interpreting the small average effects on continuous outcome measures. Other important measures such as quality of life, physical function, and institutionalization, were inconsistently reported.

Conclusions: Several brief screening instruments can adequately detect cognitive impairment, especially in populations with a higher prevalence of underlying dementia. There is no empiric evidence, however, that screening for cognitive impairment or early diagnosis of cognitive impairment improves patient, caregiver, family, or clinician decision-making or other important outcomes. Harms of screening for cognitive impairment are not well studied. In general, there is support that AChEIs and memantine and interventions that support caregivers, including those that help coordinate care for patients and caregivers, can result in small improvements in the short term. Unfortunately, the average effects of these benefits are quite small and likely not of clinical significance. Any benefits are further limited by the commonly experienced side effects of medications and the limited availability of complex caregiver interventions. Cognitive stimulation and training, exercise interventions, and other medications and supplements showed some favorable effects on patients' cognitive and physical function, but trial evidence lacked consistency and the estimates of benefit were imprecise. There is less evidence related to screening for and treating MCI. The test performance of the few instruments evaluated to detect MCI was lower than the sensitivity and specificity to detect dementia and there is little evidence for any pharmacologic or nonpharmacologic interventions to preserve or improve patient functioning in people with MCI.

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Chapter 1. Introduction

Purpose

This report will be used by the United States Preventive Services Task Force (USPSTF) to update its 2014 recommendation on screening for cognitive impairment in older adults.[1]

Condition Definition

Clinical definitions of cognitive disorders have evolved over time. In the Diagnostic and Statistical Manual of Mental Disorder Fourth Edition (DSM-IV), published in 1994, dementia was defined as a decline in two or more cognitive domains (memory, attention, language, or visuospatial or executive functioning) that affects social or occupational functioning.[2] In the DSM-5, published in 2013, dementia was subsumed under the broader category of "major neurocognitive disorder" and was defined as a decline in one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual-motor [visuospatial], or social cognition) that interferes with independence in everyday activities.[3] In the updated nomenclature, any domain could be impaired to meet the definition of dementia whereas in DSM-IV, a decline in memory was required. Furthermore, in DSM-5, a sixth cognitive domain, social cognition, was added. In both cases, these deficits do not occur exclusively during delirium, and are not better explained by another mental disorder, such as schizophrenia.

The dementia syndrome is further classified according to the symptoms and course of the impairment and the suspected underlying pathology. The major causes of the dementia syndrome are: Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia (FTD), Lewy body dementia (LBD), Parkinson's disease with dementia (PDD), and dementia of mixed etiology (most commonly AD and VaD or mixed etiology with VaD).[4] With AD, FTD, LBD, and PDD, abnormal protein deposits that accumulate in the brain are believed to contribute to deterioration of brain function and dementia (amyloid plaques, neurofibrillary tangles, Lewy bodies).[5] Other neuropathological changes associated with dementia can include cortical atrophy, hemorrhage, small-vessel ischemic disease, and neuronal and white matter loss.[6] The exact etiological mechanisms for many types of dementia (e.g., AD, FTD, LBD, and PDD), however, have not been clearly defined.[7] For example, amyloid plaques found during brain autopsies are associated with AD and LBD, but these pathological findings are not always consistent with premorbid clinical diagnoses.[8] Other established causes of dementia include depression, alcohol and other substance abuse, medications (e.g., antihistamines), metabolic disorders (e.g., thyroid disorders and diabetes), intracranial tumors, normal pressure hydrocephalus, subdural hematomas, infections (e.g., HIV, prion disease), traumatic brain or anoxic injury, and rare neurodegenerative disorders (e.g., Huntington's disease, progressive supranuclear palsy).[9, 10]

Mild cognitive impairment (MCI) is distinguished from dementia as cognitive impairment that is not severe enough to interfere with independence in daily functioning. The nomenclature for MCI is varied and includes cognitive impairment without functional impairment, cognitive impairment no dementia (CIND), mild neurocognitive disorder, and mild cognitive disorder, all

of which have varied definitions and criteria.[11] In the DSM-5, MCI is classified under the broad category of "mild neurocognitive disorder." DSM-5 criteria for MCI include concerns of cognitive impairment by the patient, informant, or clinician; findings of modest cognitive deficits; and absence of interference with daily functioning (even though greater effort or compensatory strategies may be needed).[3] This definition is consistent with that used by the International Working Group on Mild Cognitive Impairment.[12] The DSM-5 definition contrasts somewhat with earlier working definitions of MCI, including one of the most commonly used definitions of MCI published by Petersen and colleagues in 1999. The Petersen definition focuses on amnestic MCI, defined as complaints of memory impairment corroborated by an informant, memory impairment on objective testing, normal performance in non-memory cognitive domains, preserved ADLs, and no dementia.[13, 14] Some research in MCI distinguishes between amnestic and non-amnestic MCI, and between single- or multi-domain MCI.[15-17] Regardless of the nomenclature, MCI is an intermediate but not necessarily transitional cognitive state between normal cognition and dementia.

Prevalence and Burden

Dementia

Dementia is a common condition, with an estimated 2.4 to 5.5 million Americans afflicted.[4, 6, 18] The prevalence of dementia is likely underestimated given the challenges of diagnosis, particularly in primary care settings.[19, 20] By 2050, it is projected that AD will affect 13.8 million Americans, owing largely to the increase in the size of the elderly population.[21] The estimated total health, long-term, and hospice care costs for dementia in the United States were $200 billion in 2012. Medicare and Medicaid pay approximately 70 percent of those costs. These cost estimates do not include the $210 billion in uncompensated care that informal caregivers are estimated to provide annually.[22]

The prevalence of dementia was estimated at 8.8 percent in 2012 among adults 65 years or older in the United States, a significant decrease from the estimated prevalence of 11.6 percent in 2000.[23] The proportion of dementia caused by different etiologies varies widely between studies due to differences in diagnostic criteria, study setting, and age of participants. A 2017 study that used administrative enrollment and claims data from Medicare beneficiaries aged 68 years and older during the years 2011–2013 found that the most commonly defined dementia subtype was AD (accounting for 43.5% of dementia claims), followed by VaD (14.5%), LBD (5.4%), and FTD (1.0%).[24] Similarly, one systematic review found that AD accounted for 56.3 percent of cases, followed by VaD (20.3%) and mixed etiologies (6.2%).[25] Other causes, such as PDD and alcohol abuse, were much less common.[25] Only 4 percent of dementia cases were due to potentially reversible causes though only 0.6 percent of dementia cases actually reversed to normal cognition in studies that reported followup.[25]

The prevalence of dementia increases with age. In 2012, the estimated prevalence of dementia in the United States was 3.2 percent in individuals ages 65 to 74 years, rising to 9.9 percent for those ages 75 to 84 years, and 29.3 percent for those 85 years of age or older.[23] Dementia incidence also increases exponentially with age between the ages of 65 and 90 years and doubles approximately every 5 years.[26, 27] One study among nondemented older adults aged 90 year and

older found the overall incidence rate was 18.2 percent per year with rates increasing markedly with age from 12.7% per year in the 90–94-year age group, to 21.2% per year in the 95–99-year age group, to 40.7% per year in the 100+-year age group.[27]

Dementia prevalence varies by race and ethnicity. A population-based study found the prevalence of dementia in adults ages 71 years and older was 21.3 percent for blacks compared with 11.2 percent for whites.[28] Another study found that the prevalence of AD in older black adults is roughly double (10.5% vs. 5.4%) the prevalence in non-Hispanic whites,[29] while several studies have found the prevalence of AD in Hispanics to be approximately 1.5 times that observed in the white population.[28, 30, 31] 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.[30] There is little consensus, however, on the cause for observed disparities in prevalence.

Dementia prevalence also varies by gender, with more women than men affected. One study estimated that in individuals ages 71 years and older, approximately 16 percent of women had dementia compared with 11 percent of men.[22] While previous research suggested higher rates of dementia prevalence in women were related largely to women's longer life expectancy,[22] newer research suggests that differences in genetic factors[32] and education[33] levels may contribute to disparate prevalence rates by gender as well.

MCI. The prevalence of MCI is even more difficult to ascertain than the prevalence of dementia due to even greater between-study differences in sampling, methods of clinical assessment, and the criteria used to define MCI.[29] Estimates of MCI prevalence range widely, from 3 to 42 percent in adults ages 65 years and older.[34, 35] One systematic review of 35 population-based studies found the median prevalence to be 4.9 percent (range, 0.5%–31.9%) for amnestic MCI, 26.4 percent (range, 3%–42%) for MCI, and 20.6 percent (range, 5.1%–35.9%) for CIND across a broad age range of older adults.[35] While the prevalence of MCI and CIND appeared to increase with age, these studies did not identify a consistent relationship with age across different definitions.[34, 35] Likewise, these studies found no consistent relationship between MCI and gender, race/ethnicity, or education.[34, 35]

Natural History

Dementia. The most common types of dementia are irreversible and usually progressive, including AD, VaD, LBD, and FTD. Early stages of dementia generally affect instrumental activities of daily living (IADLs), such as money and medication management, shopping, or cooking, along with the ability to learn and retain new information. As the dementia progresses, patients become unable to carry out basic self-care activities of daily living (ADLs), such as dressing, toileting, or grooming.[36, 37] The onset and progression of dementia are highly variable and depend in part 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, age at diagnosis, degree of impairment, and the etiological type of dementia.[38, 39] For example, median survival time for AD is thought to be longer than for FTD, and some patients with AD can live as long as 20 years after diagnosis.[22, 40-42] 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 more rapid.[43] The rate of decline can also depend on the stage of disease, as patients may experience an accelerated rate of decline as their disease progresses.[44, 45] In addition to cognitive decline, neuropsychiatric symptoms, such as depression, anxiety, apathy, agitation, aggression, personality changes, and psychosis (e.g., delusions, paranoia, hallucinations), can occur.[6] Neuropsychiatric symptoms can occur with any type of dementia but tend to be more common with specific types. FTD, for example, is commonly associated with euphoria or disinhibition, whereas PDD and LBD are commonly associated with visual hallucinations. AD is associated with apathy, anxiety, and depression in early stages and agitation and delusions in later stages.[46-49]

MCI. The rates of stability, progression, and regression of MCI vary markedly between studies. This variation likely reflects the complex underlying pathology as well as differences in diagnostic criteria, population settings, and participants. Variations in diagnostic criteria have implications for understanding the natural history of MCI. For example, the 1999 Petersen criteria defined MCI essentially as amnestic MCI, while broader criteria used by others include categories for amnestic and nonamnestic MCI, and for single- and multidomain MCI. Each category of MCI has different predicted rates of conversion from MCI to dementia. Amnestic MCI and multidomain MCI are more likely to progress to dementia than others.[50] Additionally, 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 may also be more likely than other MCI subtypes to revert to normal cognition.[50-52]

Overall, there is strong evidence that people with MCI have a much greater risk of progressing to dementia than people with normal cognition. A 2013 systematic review found that an average of 32 percent of people with MCI go on to develop dementia over 5 years.[53] This is consistent with a 2009 meta-analysis that found that on average 38 percent of people with MCI went on to develop dementia when followed for at least 5 years.[15] In a subset of five studies included in the 2009 meta-analysis, 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 (risk ratio [RR], 13.8 [95% confidence interval [CI], 8.44 to 22.6]). Overall, the annual rate of progression from MCI to dementia (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 dementia 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.[15] Other studies using different definitions of MCI found cumulative rates of progression to dementia of 22 to 40 percent over mean study times of 5 to 10 years. MCI may also regress to normal cognition over time in 10 to 40 percent of individuals with MCI.[50, 54, 55] Although several population-based studies have noted an increased risk of mortality in people with MCI compared with those with normal cognition,[56-60] other studies have found no associated increase in mortality.[61, 62]

Risk and Protective Factors

Increasing age is the strongest known risk factor for cognitive decline in general and for AD specifically.[18] Other proposed risk factors for cognitive decline have varying levels of evidence to support an association. The ε4 allele of the lipoprotein E gene has good observational evidence in whites and Asians as a risk factor for AD.[63] Other risk factors with lower-quality

observational evidence include family history, depression, physical frailty, and low social support.[63-67]

In contrast, more years of formal education have been associated with a reduced risk of dementia, likely through multiple causal pathways, including a direct effect on brain development and function and the association between higher levels of education and positive health behaviors and better access to health care.[4, 23, 68] Likewise, better control of cardiovascular risk factors over the past decade has been associated with declining dementia risk.[23, 69, 70] Obesity has also been found to be associated with a decreased risk of dementia with the hypothesis that while obesity in mid-life may increase risk for later-life cognitive decline and dementia, obesity at older ages may be associated with cognitive and other health advantages.[71] In addition, 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 acid intake, high fruit and vegetable intake, adherence to Mediterranean diet, moderate alcohol intake, cognitive engagement, social engagement, and higher physical activity level.[72-75]

Prevention of Cognitive Impairment

There is a robust evidence base exploring the effectiveness of interventions targeting modifiable risk factors that are potentially associated with age-related cognitive decline. In 2017, a comprehensive systematic review was published by Kane and colleagues[76] on the effectiveness and harms of pharmacological and nonpharmacological interventions to prevent age-related cognitive decline, MCI, and dementia. The review, which was also subsequently published in individual manuscripts,[77-79] included 263 studies addressing 13 classes of interventions: cognitive training, physical activity, nutraceuticals, diet, multimodal interventions, hormone therapy, vitamins, antihypertensive treatment, lipid-lowering treatment, NSAIDS, antidementia drugs, diabetes treatment, and "other interventions."

Of the 13 classes of interventions examined, none of the interventions had high strength of evidence to suggest that they delayed or prevented age-related cognitive decline, MCI, or dementia. There were a few interventions types, however, that showed more potential than others in benefiting cognitive performance. For instance, the review found that some forms of cognitive training improved certain domain-specific measures of cognitive function that were targeted by the intervention (i.e., reasoning, executive function, attention, processing speed, and memory) for adults with normal cognition, but there was little evidence to support the transfer of benefits to other cognitive areas or to reduced dementia incidence. Additionally, the benefit for any form of cognitive training beyond 2 years was uncertain. Although the evidence was less compelling, physical activity and vitamin B12 plus folic acid also showed potential benefit on brief cognitive tests and memory. A few specific interventions reached moderate strength of evidence for *no* benefit in cognitive performance including vitamin E in women, angiotensin converting enzyme and thiazide, and angiotensin receptor blockers.[76]

The absence of strong and consistent evidence in support of preventive interventions to delay or reduce onset of MCI and dementia in older adults with normal cognition may largely result from limitations inherent in the included evidence. Most published trials were of limited duration and followup, ranging between 6 months and 4 years. Even at 4 years, this period is substantially

shorter than the expected latency period to reach MCI and dementia, which is thought to initiate years before participants begin to experience any symptoms. Furthermore, most randomized trials were underpowered to detect changes in the incidence of MCI and dementia due to small sample sizes.[76]

Rationale for Screening

It is estimated that 29 to 76 percent of patients with dementia or probable dementia are not diagnosed by primary care physicians.[80-82] That may be because primary care clinicians fail to recognize cognitive impairment during clinic checks that rely on routine history and physical examination.[83] Moreover, the sensitivity of a clinician's diagnosis appears to be strongly related to dementia severity, with few practitioners recognizing mild dementia.[84] Early identification of cognitive impairment, through screening, would ideally allow patients and their families to receive care at an earlier stage in the disease process, potentially facilitating discussions regarding decision-making (e.g., health care, financial, legal) while the patient still retains decision-making capacity. Clinical experts and researchers have suggested that the health, psychological, and social benefits from early recognition of dementia include: early education of patients and caregivers on the disease process; early coaching of caregivers in how to manage the patient; advanced planning (e.g., establishing a will, health care proxy, power of attorney, and advance 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.[85, 86]

Screening and Diagnostic Workup for Cognitive Impairment

Many different brief cognitive screening instruments are available to clinicians in primary care. These cognitive tests alone, however, are not diagnostic of dementia or MCI. A positive screening test triggers subsequent diagnostic testing that assesses the level and possible etiology of cognitive impairment. When dementia is suspected, the practitioner should complete a detailed and focused clinical history and physical examination. Family members or other people close to the patient who could provide an accurate history should ideally be present or contacted. This diagnostic workup may also include more comprehensive cognitive and functional assessments (e.g., neuropsychological testing or clinical evaluation by a trained clinician).

A diagnosis of dementia requires that the patient has developed requisite cognitive deficits (impairments in learning and memory, language, executive function, complex attention, perceptual-motor, or social cognition), which can be established with specific tests and interpreted relative to appropriate norms. Practitioners also can order laboratory tests to rule out potentially reversible causes of dementia (e.g., hypothyroidism, vitamin B12 deficiency). Since depression is common and treatable and often presents as cognitive impairment, it is necessary to rule it out in patients with suspected dementia. The American Academy of Neurology currently recommends structural neuroimaging with non-contrast head CT or MRI in the initial evaluation of dementia patients,[87] although the need for neuroimaging in routine cognitive workups is controversial and may be more useful for those with acute onset or rapid progression or among

those with other symptoms.[88] Genetic testing for the APOEε4 allele (which increases the risk of developing AD) is not currently recommended, nor is genetic testing for other potential causes of dementia (e.g., specific mutations) unless there is a specific characteristic family history obtained.[87, 89]

Interventions and Treatment for Cognitive Impairment

The goals of treatment for cognitive impairment are to maintain quality of life (QOL) and maximize functional performance by addressing cognitive, mood, and behavioral impairments, as well as to treat any modifiable or reversible causes of impairment. Treatment options for those with MCI and dementia are numerous and include both pharmacologic and nonpharmacologic interventions. FDA-approved pharmacologic treatments include acetylcholinesterase inhibitors (AChEIs) (i.e., donepezil, galantamine, and rivastigmine), memantine, and combination donepezil and memantine (Namzaric®). Donepezil (Aricept®) is approved for the treatment of all stages of AD, whereas galantamine (Razadyne®) and rivastigmine (Exelon®) are indicated for the treatment of mild to moderate AD and mild to moderate dementia associated with PDD (rivastigmine only). Memantine (Namenda®), on the other hand, is indicated for the treatment of moderate to severe AD. None of these medications is specifically FDA-indicated or recommended for the treatment of MCI, although they are used off-label.[90] Other medications, including antiplatelet medications, antihypertension medications, and HMG-CoA reductase inhibitors (statins), are often prescribed for cardiovascular risk reduction, primarily for the treatment of VaD or mixed dementias. Additional therapies have been tested or suggested for preventing or treating cognitive decline or the symptoms related to cognitive decline such as nonsteroidal anti-inflammatory drugs (NSAIDS), gonadal steroids, antipsychotics, anti-diabetes drugs, and dietary supplements. Experimental drug therapies include various immunotherapies targeting beta-amyloid (solanezumab), beta-secretase (verubecestat), and tau protein (AADvac1 vaccine), medications targeting inflammation in the brain (CSP-1103), intravenous immunoglobulin (IVIG), and growth hormone-releasing hormone (GHRH).[91] None of these experimental drug therapies are currently FDA-approved for use in the general population; access to these agents is restricted to individuals taking part in a clinical trial. Nonpharmacologic interventions include those targeting the patient, caregiver, or patient-caregiver dyad, and comprise multidisciplinary or multicomponent approaches, cognitive training, cognitive rehabilitation, cognitive stimulation interventions, exercise, peer support, caregiver counseling and psychoeducation, and case management.

Current Clinical Practice in the United States and Recommendations of Other Groups

Although no professional organizations explicitly recommend routine screening for dementia in asymptomatic adults (**Table 1**), many groups—including the USPSTF, Alzheimer's Association, American Academy of Neurology, American Geriatrics Society, Gerontological Society of America, U.S. Department of Veterans Affairs, Canadian Task Force on Preventive Health Care, European Federation of Neurological Societies, Royal Australian College of Practitioners, and International Association of Gerontology and Geriatrics—advise that clinicians assess the cognitive abilities of older adults who present with cognitive or cognitive-related functional

complaints.[1, 87, 92-98] The Veteran's Health Administration explicitly recommends against screening in asymptomatic adults, regardless of age, given the lack of evidence to support a benefit of identification of early cognitive impairment and adequate evidence of harms from drug therapy.[96]

In 2011, Medicare began covering "detection of cognitive impairment" as part of the new Annual Wellness Visit (AWV) benefit, which is mandated by the Affordable Care Act (ACA).[99] The AWV requires an assessment of the patient's cognitive function by direct observation with consideration of information obtained via patient reports and concerns raised by informants.[99] The cognitive assessment is intended to result in the development of a personalized prevention plan in which the provider offers feedback and educates the patient about risks, including risks for cognitive impairment, when indicated.[100] The AWV is mandated by the ACA; however, only 20 percent of the 35 million Medicare Part B enrollees had an AWV in 2016.[101] In 2013, the Alzheimer's Association published recommendations for operationalizing the detection of cognitive impairment during the AWV. It recommended the use of a brief structured assessment (i.e., the General Practitioner assessment of Cognition [GPCOG], Mini-Cog, Memory Impairment Screen [MIS], AD8, or short Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE]) if a health risk assessment reveals signs or symptoms of cognitive impairment, through clinical observation, or via concerns raised by the patient or informant.[102] Likewise, both the National Institute on Aging (NIA) (2014)[86] and Gerontological Society of America (GSA) (2016)[103] developed reference guides for primary care providers that describe the benefits of early screening, when to screen, how providers and staff can find time for screening, and how to screen for cognitive impairment. The NIA guide emphasizes and provides access to instruments that require 10 minutes or less to administer, including the AD8, Mini-Cog, and IQCODE,[86] whereas the GSA workgroup specifically endorses the Mini-Cog, GPCOG, and MIS.[103]

Previous USPSTF Recommendation

In 2014, the USPSTF concluded that current evidence was insufficient to assess the balance of benefits and harms of screening for cognitive impairment (**I Statement**).[1] At that time, the USPSTF found adequate evidence that some screening tools had sufficiently high sensitivity and specificity to be clinically useful in identifying dementia, but there was inadequate direct evidence on the benefits of screening for cognitive impairment. Additionally, while the evidence showed that several drug therapies and nonpharmacologic therapies, including those targeting caregivers, had a small effect on cognitive function and caregiver burden measures in the short term, the magnitude of the clinically relevant benefits was uncertain.

Chapter 2. Methods

Scope of Review

This review is an update of the 2013 review[104, 105] that supported the 2014 USPSTF recommendation. Our update includes studies published since the previous review and studies from the previous review that met updated inclusion criteria. We did not make any substantive changes to the scope of the review for this update other than to exclude the medication tacrine from the list of included interventions as it is no longer available in the United States.

Analytic Framework and Key Questions

With input from the USPSTF, we developed an Analytic Framework (**Figure 1**) and five Key Questions (KQs) to guide the search and selection of studies, data abstraction, and data synthesis.

Screening Key Questions (KQs 1–3)

1. Does screening for cognitive impairment in community-dwelling older adults in primary care–relevant settings improve decision-making, patient, family/caregiver, or societal outcomes?
2. What is the accuracy of screening instruments to detect cognitive impairment in community-dwelling older adults?
3. What are the harms of screening for cognitive impairment in community-dwelling older adults?

Treatment/Management Key Questions (KQs 4, 5)

4. Do interventions for mild to moderate dementia or mild cognitive impairment in community-dwelling older adults improve decision-making, patient, family/caregiver, or societal outcomes?
5. What are the harms of interventions for mild to moderate dementia or mild cognitive impairment in community-dwelling older adults?

Data Sources and Searches

First, we reviewed all included studies in the previous review,[104, 105] including those that were part of a systematic review that was previously used in its entirety.[106] Next, we searched the following databases to identify English-language literature published between January 2012 and January 2019: Ovid MEDLINE, PubMED (for publisher-supplied records only), PsycInfo, and the Cochrane Central Register of Controlled Trials. A research librarian developed and executed the search, which was peer-reviewed by a second research librarian (**Appendix A**). We supplemented our searches by examining the reference lists of other previously published reviews, meta-analyses, and primary studies and from suggestions from experts. We also

searched ClinicalTrials.gov for ongoing trials related to KQ 1, and have conducted ongoing surveillance for relevant literature for all bodies of evidence through June 2019. We imported the literature from these sources directly into EndNote® X9 (Thomson Reuters, New York, NY).

Study Selection

We developed specific criteria to guide our study selection (**Appendix A Table 1**).

Population

For all KQs, we included studies that were relevant to community-dwelling, noninstitutionalized adults ages 65 years and older being seen in primary care in the United States. For screening studies, we excluded studies conducted among patients in hospitals or nursing homes (i.e., skilled nursing facilities, rehabilitation facilities, and intermediate care facilities) or in which patients were selected from referred settings (e.g., memory, neurology, psychogeriatric, Alzheimer's Disease Research Centers). We included only treatment studies conducted among community-dwelling older adults with MCI or mild to moderate dementia. We excluded treatment studies that focused on patients with severe dementia, as most severe cases would likely be clinically identified rather than screen detected. We also excluded primary prevention trials in which treatment was aimed at preventing or delaying the onset of cognitive impairment in older adults without known cognitive impairment.

Screening Instruments

For KQs addressing screening, 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. Screening instruments could be administered to the patient or an informant (family member or caregiver), and take place in person, by telephone, or online. We excluded screening done by diagnostic imaging or biomarker testing.

Interventions and Comparators

For KQs addressing the treatment of cognitive impairment, we focused on major pharmacologic and nonpharmacologic interventions intended for use during the early and mild stages of cognitive impairment and aimed at improving patient cognition, physical function, QOL, or to improve caregiver burden or well-being, or a combination of these. We excluded interventions with a primary aim of improving patient behavioral and psychological symptoms of dementia, improving physical performance, or reducing falls. A full list of included and excluded interventions is included in **Appendix A Table 1**.

Comparator interventions included no treatment or waitlist, placebo, usual care, or attention controls. Attention controls included minimal support and "sham" cognitive activities (e.g., working on puzzles, reading the newspaper) or exercise interventions (e.g., light stretching). Usual or standard treatment refers to what would normally be provided in the study setting to participants with dementia, and might include medication, clinic consultations, contact with a

community mental health team, or support from voluntary organizations. We excluded studies comparing two active interventions with no true control group as the focus of this review was not on the comparative effectiveness of various interventions.

Outcomes

We included studies examining the benefits or harms of screening or treatment that reported outcomes on decision-making for patients and families or clinicians (e.g., health care planning, including advance directives; screening and diagnostic decisions; safety planning; legal and financial planning); patient health outcomes (i.e., mortality, health care utilization, institutionalization, global function, cognitive function, physical function, QOL, and neuropsychiatric symptoms including depression and anxiety); caregiver outcomes (i.e., caregiving burden, symptoms of depression and anxiety, QOL); or societal outcomes (e.g., automobile accidents). We excluded studies if they included only patient satisfaction or cost outcomes. For harms, we included studies reporting total adverse events (AEs), withdrawals due to AEs, and serious adverse events (SAEs) that resulted in unexpected medical care, morbidity, or mortality.

Study Design

For KQs 1 and 3, we included randomized and nonrandomized controlled trials that compared individuals who received screening with those who received no screening or usual care. For studies of test accuracy of screening tests (KQ 2), we included studies that reported the sensitivity and specificity (or data that would allow us to calculate the sensitivity and specificity) of a screening test compared with a diagnostic reference standard (i.e., clinical assessment or neuropsychological testing, with explicit diagnostic criteria with or without expert consensus/conference). Studies designed to develop a screening instrument (rather than validate a screening instrument) were excluded unless they had a separate study sample to validate the instrument. We excluded case-control studies and studies that selectively recruited patients with known or clinically suspected dementia or MCI (or cognitively normal controls) due to the high risk of bias in patient selection for these studies. We did, however, include studies among patients with subjective memory complaints (not clinically suspected) because subjective memory complaints are relatively common among older adults.[107]

Treatment effectiveness studies (KQ 4) were limited to randomized clinical trials (RCTs) or nonrandomized clinical trials. For harms (KQ 5), we included all trials that were included for the effectiveness question (KQ 4), and cohort or case-control studies with $n \geq 1{,}000$. We excluded open-label extension data because there was not a comparison group.

Because of the large volume of search results, we used a single-screen process (i.e., one reviewer screened for exclusion) for records with terms clearly outside of the scope of the review in the title or abstract (e.g., “mice,” “HIV,” “brain injury”). Two independent reviewers then screened the titles and abstracts, using the inclusion and exclusion criteria as a guide, of all other records and those not flagged for exclusion during single screening. Subsequently, at least two reviewers assessed the full text of potentially relevant studies using a standard form that outlined the eligibility criteria. Disagreements were resolved through discussion and consensus. Title and

abstract and full-text review were conducted in DistillerSR (Evidence Partners, Ottawa, Canada). We kept detailed records of all included and excluded studies (and the reason for their exclusion) during full-text review.

Quality Assessment

At least two reviewers critically appraised all newly identified eligible studies in DistillerSR. We assigned each study a quality rating of "good," "fair," or "poor" according to the USPSTF's study design-specific criteria.[108] We supplemented these criteria with items from the Newcastle-Ottawa Scale for cohort studies[109] and the Quality Assessment of Diagnostic Accuracy Studies I and II for studies of diagnostic accuracy[110, 111] (**Appendix A Table 2**). Disagreements were resolved by consensus and, if needed, consultation with a third independent reviewer. Because this review was an update of our own work, we did not repeat critical appraisal of the original studies through full dual-quality rating; rather, we confirmed the quality rating during data abstraction. Likewise, we did not systematically critically appraise all of the studies that were previously identified and included from a related systematic review.[106] In that review, the methodological quality of the included studies was assessed using a modified Jadad scale and included only studies with a minimum score of 3. We critically appraised only studies that scored a 3 of 5 on the Jadad scale to examine whether they were at high risk of bias.

Good-quality studies were those that met nearly all specified quality criteria. For studies of test accuracy, we assigned a good-quality rating if they recruited patients consecutively or randomly, administered the index test blinded to, or at least prior to, the reference standard, used a reference standard that could accurately classify the target condition, interpreted the reference standard independently from the screening test, and administered the screening test and reference standard on the same day to all participants. For treatment studies, we rated them as good quality if comparable groups were assembled initially and maintained throughout the study, reliable and valid measurement instruments were used and applied equally to the groups, procedures for maintaining fidelity to the intervention were in place, followup was adequate (i.e., ≥80% retention overall) and not differential between groups, data were complete, and there was no evidence of selective reporting. Fair-quality studies did not meet these criteria but did not have serious threats to their internal validity related to the design, execution, or reporting of the study.

Studies rated as poor quality had several important limitations or one critical flaw and were excluded from this review. The most common potential risk of bias for diagnostic studies that warranted a poor-quality rating was application of the reference standard to only those patients who screened positive. In these kinds of cases, when missing data are not random, analysis will generate biased estimates of diagnostic accuracy,[112-115] and verification of only screen-positive patients will generally lead to an overestimation of both sensitivity and specificity. Potential risk-of-bias for treatment trials resulting in poor quality ratings included very high attrition (>40%) or differential attrition (>15% between groups), no data on the number of participants with complete data or reasons for missing data, and unclear randomization procedures coupled with imbalances in baseline characteristics between groups.

Data Abstraction

For screening studies (KQ 2), we extracted details about each study's screening instrument(s) (e.g., administration time, language, cut-point); recruitment and inclusion criteria; number of participants approached and analyzed; patient characteristics (i.e., age, sex, race/ethnicity, socioeconomic status [SES]); prevalence of dementia and/or MCI; reference standard details; and diagnostic outcomes for given cut-points (i.e., contingency table, sensitivity, specificity, positive and negative predictive values, area under the curve). When more than one cutoff was reported for a screening instrument, only the optimal cutoff (as indicated by the author or as assessed by the reviewer as the best balance of sensitivity and specificity) was abstracted. For the MMSE, cutoffs of 23, 24, 23/24, or 24/25 were always abstracted.

For treatment trials (KQs 4-5), we extracted details about each study's design (e.g., recruitment and inclusion criteria, number of participants recruited and analyzed); patient characteristics (e.g., proportion with MCI or specific dementia syndromes, age, sex, race/ethnicity, SES); and intervention characteristics (e.g., intervention components, dose/intensity, frequency and duration, interventionists) and control groups. For all outcomes, if a study reported results at more than one followup time point, we abstracted data for all time points at 3 months' followup or longer. Results related to the following outcomes were abstracted: any decision-making outcome (on behalf of the clinician, caregiver, or patient); any societal outcome; patient mortality; institutionalization; health care utilization including hospitalizations and emergency department visits; global function (e.g., Clinical Dementia Rating [CDR], Clinician's Interview-Based Impression of Change – Plus [CIBIC+]); global cognitive function and domain-specific cognitive function; physical function (i.e., activities of daily living and instrumental activities of daily living); patient and caregiver QOL, psychological morbidity, depressive symptoms, and anxiety symptoms; neuropsychiatric symptoms; measures of caregiver burden; and adverse events. A table of the most commonly reported instruments for each outcome, including a description, is provided in **Appendix A Table 3**. Given the already complex nature of this review, we did not abstract caregiver outcomes related to caregiving self-efficacy, caregiving competence or mastery, time spent caregiving, and other measures of perceived needs, mood, or satisfaction with caregiving.

For measures of global cognitive function, we abstracted the Alzheimer's Disease Assessment Scale (ADAS-Cog) as the primary measure and 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, TICS). We abstracted results for domain-specific cognitive function measures (i.e., executive function, memory, attention, and language) qualitatively for each measure in order to compare these results to measures of global cognitive function. For QOL outcomes, we included measures of general QOL (e.g., Short-Form 12 and 36 [SF-12 and SF-36], EuroQol 5-Dimensions [EQ-5D]) and dementia-related QOL (e.g., Dementia Quality of Life [DQOL], Dementia Quality of Life [DEMQOL], Quality of Life in Alzheimer's Disease [QOL-AD]). We only abstracted results for neuropsychiatric symptoms for depression, anxiety, overall psychological morbidity, and composite behavioral and symptoms (e.g., total scores on the Neuropsychiatric Inventory [NPI], frequency scores on the Revised Memory and Behavior Problems Checklist [RMBPC]). Given

the focus of the review and overall volume of results, we did not abstract results for other specific neuropsychiatric symptoms such as agitation, hallucinations, and insomnia.

We abstracted data from each included study into detailed abstraction forms using DistillerSR. One reviewer completed primary data abstraction, and a secondary reviewer checked all data for accuracy and completeness. We contacted authors when data reporting was incomplete, or data points required clarification. In cases where data was only presented in graphical format, we used WebPlotDigitizer© Version 3.10 to extract data and provide estimates of the within-group means and variance at followup. Such data was not abstracted if only group means (and not measures of dispersion or between-group differences) were displayed.

Data Synthesis and Analysis

For test accuracy studies (KQ 2), our primary outcomes of interest were sensitivity and specificity. We synthesized 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. We categorized these instruments as very brief (administered in ≤5 minutes), brief (administered in 6 to 10 minutes), or longer, self-administered instruments (>10 minutes). We relied on published administration times or administration times reported in the individual studies.

We reported the sensitivity and specificity for the most commonly accepted or reported cutoffs. While we also extracted positive and negative predictive values, we did not focus on these measures because the prevalence of cognitive impairment varied widely across studies. Test performance was either directly extracted from individual study results, calculated using study presented contingency tables, or calculated using the prevalence of cognitive impairment and the reported sensitivity and specificity. We summarized ranges of sensitivity and specificity for each instrument and used figures to visually display the data, as we were unable to quantitatively pool most data given the limited number of studies per instrument by condition, heterogeneity in population or diagnostic criteria, or lack of reporting about cutoffs (and scoring). We conducted quantitative synthesis for only one instrument: the MMSE at a cutoff of 23 or 24 to detect dementia. We ran a bivariate model, which modeled sensitivity and specificity simultaneously, thus accounting for the correlation between these variables.

For treatment trials, we grouped the interventions into four broad categories: 1) FDA-approved medications to treat AD (i.e., AChEIs and memantine); 2) other medications or dietary supplements (e.g., NSAIDs, gonadal steroids, and vitamins); 3) nonpharmacologic interventions aimed primarily at the patient, including: cognitive training, stimulation, and/or rehabilitation; exercise interventions; and multicomponent and other interventions; and 4) nonpharmacologic interventions aimed primarily at the caregiver or caregiver-patient dyad including psychoeducation, care and case management, and other caregiver-focused interventions. Given that there is no agreed-upon classification system for grouping or describing nonpharmacologic interventions,[116] we classified interventions based on the content of the intervention and intended audience, using available taxonomies and definitions where available. We categorized interventions based on how they were described in each study in relation to our working definitions rather than how they were named or classified in the study. We acknowledge that our

categorization scheme represents broad definitions, that there may be some overlap between categories, and that our assignments may not be precise. Nonetheless, given the volume and heterogeneity of evidence, such categorization helped to adequately synthesize and interpret results.

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. We created summary tables to capture the key study characteristics and sources of clinical heterogeneity as well as intervention characteristics for each body of evidence. Additionally, we created tables for each body of evidence that display a summary of results for each primary outcome within that body of evidence. In these summary tables, we focus on the longest duration of followup for each trial.

We conducted meta-analyses on the most commonly reported outcomes for each body of evidence. As a result, pooled analyses were conducted for FDA-approved medications on global cognitive function outcomes, global function outcomes, and harms; for nonpharmacologic patient-level interventions for global cognitive function outcomes; and for caregiver and caregiver-patient dyad interventions for caregiver burden and caregiver depression measures. For consistency across the body of evidence, in quantitative analyses we focused on 6- to 12-month outcomes and included only shorter- or longer-term results when 6- or 12-month outcomes were not available. When more than one treatment group was included in a study, we selected the group that provided the treatment most like that described in other studies for the meta-analyses.

We ran random-effects models using the DerSimonian and Laird (DL) method.[117] For analyses with fewer than 10 trials, we also ran a sensitivity analysis using a more conservative restricted maximum likelihood (REML) analysis with the Knapp-Hartung correction for small samples.[118] Our summary table reflects the results of these more conservative analyses, including the standard deviation of the effect size, Tau. In cases where continuous outcomes were measured using a variety of different instruments with differing scales (e.g., caregiver burden), we analyzed a standardized effect size (Hedge's g) based on the differences in change between groups from baseline to followup. A pooled risk ratio (for binary data) was used to analyze harms outcomes and improvement or maintenance in global function for AChEIs and memantine interventions. When trials only reported results separately for subgroups (e.g., patients with dementia and patients with MCI), we included entries for both subgroups in the meta-analysis.

We examined the association between key study characteristics and effect sizes when possible. This included study quality (i.e., good vs. fair), population characteristics (i.e., age, dementia vs. MCI, and baseline MMSE scores), setting (United States vs. other country), intervention characteristics (i.e., duration of intervention, group- vs. non-group-based cognitive-focused activities), and control conditions (no intervention or usual care vs. sham or minimal interventions). In quantitative analyses with at least 10 trials, we used meta-regressions to explore heterogeneity in effect sizes. For analyses with fewer trials or no quantitative analysis, we visually inspected the results for any patterns of effects. 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. Finally, for outcomes with 10 or more trials in

the meta-analysis, we generated funnel plots and ran an Egger's test to evaluate small study effects and potential publication bias.[119, 120]

We used Stata version 15.1 (StataCorp LP, College Station, TX) for all analyses. All significance testing was two-sided, and results were considered statistically significant if the p-value was 0.05 or less.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each KQ. We adapted the Evidence-based Practice Center (EPC) approach,[121] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation Working Group.[122] Our method explicitly addresses four of the five EPC-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations). We did not address the fifth required domain—directness—as it is implied in the structure of the KQs (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

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

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

Expert Review and Public Comment

A draft Research Plan was posted on the USPSTF Web site for public comment from June 29 to July 26, 2017. In response to public comment, the USPSTF provided a definition for MCI, clarified the specific etiologies of dementia that would be included, and clarified that studies conducted exclusively among people with potential reversible causes of dementia would be excluded. A final research plan was posted on the USPSTF Web site on October 19, 2017. We made no deviations from the final research plan in the conduct of this review.

USPSTF Involvement

We worked with four USPSTF members at key points throughout this review, particularly when determining the scope and methods and developing the Analytic Framework and KQs. The USPSTF members approved the final Analytic Framework, KQs, and inclusion and exclusion criteria after revisions reflecting the public comment period. AHRQ funded this review under a contract to support the work of the USPSTF. An AHRQ Medical Officer provided project oversight, reviewed the draft report, and assisted in the external review of the report.

Chapter 3. Results

We reviewed 8,397 abstracts and 845 articles for all KQs (**Appendix B**). Overall, we included 286 studies representing over 280,000 older adults. Ninety-one studies were newly identified in this update and 195 were carried forward from the preview review. Consistent with the previous review, no published studies were included that addressed the benefits and harms of screening (KQs 1 and 3). We included 59 studies (8 of which were new) that addressed the test accuracy of screening instruments (KQ 2) and another 224 trials (82 new) and 3 observational studies (1 new) that addressed the benefits and harms of treatment (KQs 4-5).

The lists of included studies and excluded studies (with reasons for exclusion) are available in **Appendix C** and **Appendix D**, respectively. Across all KQs, eight studies included in the previous review were excluded for poor quality upon re-review and an additional 36 new studies were excluded for poor quality due to several methodological issues (**Appendix D**).

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

No published trials examined the direct effect of screening for cognitive impairment on patient, caregiver, or societal outcomes, including decision-making outcomes. There is, however, one recently completed large trial (the CHOICE study, NCT01699503) that, per its protocol, is designed to contribute information about the benefits, harms, and costs of routine screening for dementia among older adults ages 65 and older in primary care in the United States.[123] This trial was specifically designed and funded to address the lack of empirical data included in the previous USPSTF review. We discuss this trial, including our plans to incorporate its findings, in more detail below when discussing results for KQ 1.

We identified 59 studies that address the test accuracy of screening for MCI or dementia. Most of these studies were included in the prior USPSTF review; only eight studies were new. 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 longer, self-administered tests (>10 minutes). We included 25 very brief instruments, 20 brief instruments, and 4 longer, self-administered instruments. All 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 tested in a few well-designed studies in populations generalizable to primary care. The tests most relevant to screening in primary care are very brief instruments, with an administration time of 5 minutes or less. Eight very brief instruments were examined in more than one study (CDT, Lawton IADL, MIS, MSQ, Mini-Cog, VF, AD8, FAQ), with sensitivity to detect dementia usually at 0.75 or higher (range 0.43 to 1.0) and specificity at 0.80 or higher (range 0.54 to 1.0). The MMSE, a brief test taking 7-10 minutes to complete, remains the most studied instrument (k=32), but the administration time is longer than ideal for a first

step of screening for cognitive impairment in primary care. For the MMSE, the most commonly reported cut-points to detect dementia were ≤23 and ≤24, although higher and lower cut-points were evaluated in various studies. Pooled estimates across 15 studies (n=12,796) resulted in a sensitivity of 0.89 (95% CI, 0.85 to 0.92) and a specificity of 0.89 (95% CI, 0.85 to 0.93) at a cut-point of ≤23 or ≤24 for the MMSE. The range of sensitivity contributing to the pooled analysis was 0.77 to 1.0, and the range of specificity was 0.71 to 0.99. Even at cutoffs not pooled, the sensitivity remained at 0.75 or higher for all but one study and the specificity was 0.70 or higher for all but one study. The test accuracy of the MMSE to detect MCI was based on a much smaller body of literature (k=13) with a variety of cutoffs, and resulted in less consistent estimates for test accuracy, with a range in sensitivity from 0.20 to 0.93 and range in specificity from 0.48 to 0.93. The test accuracy of five additional brief tests (7MS, AMT, MoCA, SLUMS, TICS) was reported in more than one study, with sensitivity to detect dementia ranging from 0.74 to 1.0 and specificity ranging from 0.65 to 0.96. For self-administered, longer tests, only one instrument (the IQCODE) was assessed in more than one study, with sensitivity to detect dementia ranging from 0.80 to 0.88 and specificity ranging from 0.51 to 0.91. Across all instruments, test performance was generally higher in the detection of dementia versus mild cognitive impairment, although confidence intervals overlapped. Brief instruments appear to have slightly better test performance in detecting MCI and dementia than very brief instruments although, this difference is likely not statistically significantly different.

No studies directly addressed the adverse psychological effects of screening or adverse effects from false-positive or false-negative testing, although again, we expect the recently completed CHOICE study to contribute answers to this question.

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

Consistent with the previous review, we did not identify any published trial evidence that addressed whether screening in primary care has an impact on patient, family, clinician, or societal outcomes, including decision-making.

Per its published protocol, one recently completed U.S.-based large trial (NCT01699503) meets inclusion criteria for this review and is expected to contribute evidence to answer this question.[123] Scientists from the Indiana University Center for Aging Research and Regenstrief Institute conducted a randomized controlled dementia screening trial called the CHOICE trial (Cognitive Health Outcomes Investigation of the Comparative Effectiveness). The trial was funded by the National Institute of Aging to provide empiric evidence to address this gap in the literature, as identified in the previous USPSTF review and recommendation. Within this trial, approximately 4,000 individuals ages 65 years and older without a diagnosis of dementia, cognitive impairment, or serious mental illness receiving care at primary care practices within two cities in Indiana were randomized to either screening for dementia using the very brief screening tool, MIS-T, or no screening for dementia. Adults who screened positive for dementia and were subsequently found through diagnostic assessment to have dementia were referred to

the local Aging Brain Care program, which delivers an evidence-based collaborative care model for dementia and depression and is modeled after one of the care management trials included in our review. Primary outcomes, measured at 1, 6, and 12 months, included patients' health-related QOL, mood, and anxiety. The intended secondary outcome was the cost effectiveness of dementia screening in primary care. Measures of advance care planning information (e.g., having power of attorney for health care and/or financial affairs, having a living will, and having life and additional insurance policies) were also intended to be captured. The trial is registered as complete as of November 2017 and published results are expected in 2019. Our hope is to include the findings from this study in the final version of this review.

Key Question 2. What Is the Accuracy of Screening Instruments to Detect Cognitive Impairment in Community-Dwelling Older Adults?

We identified 59 studies (n=38,531) that addressed the accuracy of cognitive impairment screening instruments (**Appendix C**);[124-180] eight of these studies were newly identified and the other 51 were included in the previous review (**Table 2**).

Study and Population Characteristics

Approximately half of the studies (k=25) were conducted in the United States. The remainder were conducted in Germany (k=6), Australia (k=4), the United Kingdom (k=4), Spain (k=3), France (k=3), South Korea (k=3), Finland (k=2), Ireland (k=2), Taiwan (k=2), and Canada, the Netherlands, Hong Kong, Singapore, and Sweden (1 each). The number of participants screened ranged from 46 to 8805. Thirty-four studies recruited fully or partially from the community and 23 recruited partially or fully from primary care. The remaining two studies recruited patients from either an insurance list[162] or ex-servicemen who were prisoners of war in Japan during World War II.[151] Forty-seven of the 59 studies reported the test accuracy to detect dementia and 35 reported the test accuracy to detect cognitive impairment (inclusive of MCI as well as MCI and dementia combined). Among the 59 studies, the prevalence of cognitive impairment varied widely; dementia ranged from 1 to 47 percent (k=51), mild cognitive impairment (k=29) ranged from 10 to 52 percent, and the prevalence of cognitive impairment (inclusive of MCI and dementia, k=22) ranged from 17 to 90 percent. Mean age ranged from 68 to 95. Percent female ranged from 0 to 100. Race/ethnicity was only reported in 21 studies; six were predominantly or entirely Asian, 11 were predominantly or entirely white, three were predominantly or entirely black, and one was fairly evenly distributed between white, black, and Hispanic. Education was reported in 22 studies with a wide range of education levels; mean years of education ranged from 5 to 16 and those with more than a high school education ranged from 4 to 73 percent.

Instrument and Reference Standard Characteristics

We categorized the screening tests by administration time: very brief (≤5 minutes), brief (6-10 minutes), and longer (>10 minutes, self-administered) (**Table 3**). Of the 59 included studies, 49 screening tests were evaluated. Very few were evaluated in more than one study. Full names that correspond to instrument abbreviations are provided in **Table 3.** Most of the tests (25) fall into

the very brief (≤5 minutes) category. The very brief tests are: 3-Word, 6-Item Screener, AD8, CDT, CoDEx, Dubois 5-Word, FAQ, GPCOG, HVLT, single-item informant memory report, Katz ADL, Lawton IADL, M@T subtests, MF-2, Mini-Cog, MIS/MIS-T, MSQ/SPMSQ, OMC, self-reported subjective memory impairment, STMS, Sweet 16, TMT, TYM subtests, VAT, and VF. The brief tests (20 tests) are: 7MS, AMT, FCR, FOME-abbreviated, Immediate recall, Kendrick, Labyrinth, M@T, MMblind, MMSE, MoCA, OT, SBT, SLUMS, SMMSE, Storandt, TICS/TICS-M, TYM, and Word List Learning, and Word List Recognition. The longer tests (4 tests) are: CAMCI, CAST, CIDS/SCIDS, and IQCODE/Short IQCODE. The tests were typically administered by clinical staff; in a few cases, they were self-administered. Most of the screening instruments directly assessed the cognitive function of the patient (with a few also evaluating physical function), but five queried only the informant (IQCODE, CIDS, FAQ, AD8, and single-item informant memory report), and one collected information from the patient and informant (GPCOG). The cognitive domains assessed varied, but most of the tests addressed memory.

The reference standard used to diagnose dementia or MCI usually consisted of a neuropsychological battery of tests and often was supplemented by a clinical examination, laboratory testing, imaging, assessment of depression and physical function, and/or an informant interview. The reference standard was administered by research staff, neurologists, psychiatrists, psychologists, psychometricians, physicians, and/or nurses, and the diagnosis was usually made by consensus. DSM-IV, DSM-III-R, or DSM-III criteria were most often used to diagnose dementia, sometimes in conjunction with NINCDS-ADRDA[181] (for Alzheimer's) and NINDS-AIREN[182] (for vascular dementia) criteria. No studies used DSM-5 criteria. MCI was more variably diagnosed, with criteria including that from the International Working Group on MCI,[12] performance ≥1 or 1.5 SD below normal, performance <10th percentile in at least one cognitive test, a CDR of 0.5, reported impairment that did not meet the criteria for dementia, criteria developed by Petersen,[183] criteria developed by a specific ADRC, or NINCDS-ADRDA (for amnestic MCI).

We rated10 studies as good quality and 49 studies as fair quality. Studies that were rated fair quality had a higher risk of bias due to patient selection (volunteers or limited information on how patients were recruited), partial verification (only a subset of participants who screened negative received the full reference standard), incorporation (the screening test was one of the tests included in the reference standard or not independently administered), or disease progression (a lag between the administration of the reference standard and the screening test).

Below we report the test accuracy results grouped by category of screening instrument based on test administration time. Results for all instruments, including those only evaluated in one study, are presented in **Tables 4**–**6**. Narrative results are only provided for instruments that were evaluated in more than one study.

Very Brief Instruments (≤5 minutes)

The accuracy of 25 very brief screening tests to identify dementia or cognitive impairment was evaluated in 31 studies (n=22,359) (**Table 4**). Only eight very brief tests were reported in more than one study (**Figure 2**). Very brief tests evaluated in only one study are shown in **Figure 3**; these tests had wide variation in sensitivity and specificity and are not discussed in detail. The eight tests evaluated in at least two studies included six tests administered to patients: the CDT

(k=9), MIS/MIS-T (k=5), MSQ/SPMSQ (k=4), Mini-Cog (k=4), verbal fluency (k=6), Lawton IADL (k=2), and two that were informant-based: the AD8 (k=3) and FAQ (k=2). Among all very brief screening tests, sensitivity was generally higher in the detection of dementia compared with the detection of cognitive impairment (inclusive of MCI alone or MCI and dementia diagnoses), although the confidence intervals often overlapped, and the cutoffs were not always adjusted to identify a lower level of impairment. Sensitivity and specificity to detect dementia was above 0.75 (range 0.43 to 1.0) and 0.80 (range 0.54 to 1.0) (respectively) for most studies, while sensitivity and specificity to detect cognitive impairment (MCI alone or MCI and dementia diagnoses) was less consistent.

For the CDT, the sensitivity to detect dementia ranged from 0.75 to 0.98 (95% CI range, 0.61 to 1.0) and specificity ranged from 0.81 to 0.94 (95% CI range, 0.76 to 0.97) (k=4). To detect cognitive impairment, sensitivity ranged from 0.41 to 0.85 (95% CI range, 0.34 to 0.97) and the specificity ranged from 0.44 to 0.83 (95% CI range, 0.33 to 0.87) (k=4). For the Mini-Cog (the CDT plus 3-item word recall), sensitivity ranged from 0.76 to 1.0 (95% CI range, 0.54 to 1.0) to detect dementia (k=4) and from 0.39 to 0.84 (95% CI range, 0.34 to 0.88) to detect cognitive impairment (k=3). Specificity ranged from 0.54 to 0.85 (95% CI range, 0.43 to 0.88) to detect dementia (k=4) and from 0.73 to 0.88 (95% CI range, 0.45 to 0.92) to detect cognitive impairment (k=3). Two studies evaluated the Lawton IADL at various cutoffs (≤4 and 6.5); sensitivity ranged from 0.89 to 0.91 (95% CI range, 0.81 to 0.96) and specificity ranged from 0.81 to 0.86 (95% CI range, 0.80 to 0.89). For the MIS/MIS-T at a cutoff of ≤4, sensitivity to detect dementia ranged from 0.43 to 0.86 (95% CI range, 0.24 to 0.94) and specificity ranged from 0.85 to 0.97 (95% CI range, 0.82 to 0.99) (k=5). Test accuracy did not differ by version (MIS versus MIS-T), but the study with the lowest prevalence of dementia had the poorest performance. Only one study evaluated the MIS (4-item free and cued recall) to detect cognitive impairment, with sensitivity of 0.17 (95% CI, 0.13 to 0.22) and specificity of 0.98 (95% CI, 0.96 to 0.99) using the same cutoff of ≤4. The MSQ and the SPMSQ (a shorter version derived from the MSQ) were only evaluated to detect dementia with a range in sensitivity of 0.92 to 1.0 (95% CI range, 0.44 to 1.0) and range in specificity of 0.83 to 1.0 (95% CI range, 0.76 to 1.0) (k=4). Test performance did not differ by the version (MSQ versus the shorter version derived from the MSQ, the SPMSQ). For verbal fluency tests (category or names), sensitivity to detect dementia ranged from 0.68 to 0.98 (95% CI range, 0.48 to 1.0) and specificity ranged from 0.81 to 0.89 (95% CI range, 0.76 to 0.92) (k=5). These studies did not examine the test accuracy to detect cognitive impairment using verbal fluency tests.

Two very brief instruments queried the informant—the AD8 and the FAQ. The AD8 was evaluated in three studies and the FAQ in two. The sensitivity of the AD8 to detect dementia ranged from 0.88 to 0.91 (95% CI range, 0.79 to 0.96) and the specificity ranged from 0.84 to 0.91 (95% CI range, 0.83 to 0.94) (k=2). To detect cognitive impairment, the sensitivity ranged from 0.74 to 0.85 (95% CI range, 0.62 to 0.90)—the lower value corresponding to the assessment of MCI without dementia and the upper value corresponding to cognitive impairment inclusive of MCI and dementia—and the specificity was the same for both at 0.86 (95% CI, 0.78 to 0.91). The sensitivity of the FAQ to detect dementia ranged from 0.87 to 0.94 (95% CI range, 0.62 to 0.98) and the specificity ranged from 0.82 to 0.84 (95% CI, 0.75 to 0.88). To detect cognitive impairment, the sensitivity was 0.73 (95% CI, 0.63 to 0.81) and the specificity was 0.73 (95% CI, 0.61 to 0.82).

Brief Instruments (6–10 Minutes)

The accuracy of 20 brief screening tests to identify dementia or cognitive impairment was evaluated in 48 studies (n=29,950) (**Table 5**). Only six brief tests were evaluated in two or more studies (**Figure 4**). The other 14 brief tests evaluated in only one study are shown in **Figure 5**. All six tests that were evaluated in at least two studies were administered to patients and include: the MMSE (k=32), 7MS (k=2), AMT (k=5), MoCA (k=5), SLUMS (k=2), and TICS/TICS-M (k=4).

The instrument most widely evaluated in the included studies was the MMSE (k=32; n=25,209). The bivariate pooled analysis for the MMSE at a cutoff of ≤23 or ≤24 to identify dementia (≤23 is the recommended cutoff) resulted in a sensitivity of 0.89 (95% CI, 0.85 to 0.92; I^2=73.8%) and a specificity of 0.89 (95% CI, 0.85 to 0.93; I^2=97.7%) (k=15, n=12,796) (**Figure 6**). At cutoffs that were not pooled (≤18 to ≤29.5), the sensitivity of the MMSE to detect dementia ranged from 0.38 to 1.0 (95% CI range, 0.18 to 0.99) and the specificity ranged from 0.67 to 0.96 (95% CI range, 0.53 to 0.99) (**Figure 7)**. To detect cognitive impairment, and at a variety of cutoffs (≤20 to ≤29.5), the sensitivity ranged from 0.20 to 0.93 (95% CI range, 0.06 to 1.0) and specificity ranged from 0.48 to 0.93 (95% CI range, 0.42 to 0.97). Use of a higher cut-off (i.e., higher than the recommended ≤23) does not appear to increase the ability to detect cognitive impairment. The study with the poorest test performance (sensitivity of 0.48 and specificity of 0.48) used a very high cutoff (≤29.5 out of a score of 30).

Five additional brief tests were evaluated in more than one study (**Figure 4**). The sensitivity of the 7MS (n=553) to detect dementia was 1.0 in two studies (95% CI range, 0.77 to 1.0) and specificity ranged from 0.95 to 0.96 (95% CI range, 0.91 to 0.98). For the AMT, sensitivity to detect dementia ranged from 0.92 to 1.0 (95% CI range, 0.16 to 1.0) and the specificity ranged from 0.83 to 0.95 (95% CI range, 0.68 to 0.99) (k=2). For the MoCA, sensitivity to detect dementia ranged from 0.78 to 1.0 (95% CI range, 51 to 1.0) and specificity ranged from 0.65 to 0.94 (95% CI range, 0.55 to 0.96) (k=4). To detect cognitive impairment, sensitivity ranged from 0.72 to 0.94 (95% CI range, 0.58 to 0.97) and specificity ranged from 0.75 to 0.84 (95% CI range, 0.61 to 0.90) (k=3). For the SLUMS, to detect dementia, sensitivity for two education subgroups (with different cutoffs selected for each group) ranged from 0.98 to 1.0 (95% CI range, 0.88 to 1.0) and specificity ranged from 0.65 to 0.69 (95% CI range, 0.61 to 0.75). To detect cognitive impairment, sensitivity ranged from 0.74 to 0.95 (95% CI range, 0.61 to 0.98) and specificity ranged from 0.65 to 0.87 (95% CI range, 0.51 to 0.91) (k=2). For the TICS/TICS-M, sensitivity to detect dementia ranged from 0.74 to 0.88 (95% CI range, 0.55 to 0.95) and specificity ranged from 0.87 to 0.93 (95% CI range, 0.83 to 0.95) (k=2). To detect cognitive impairment, sensitivity ranged from 0.71 to 0.82 (95% CI range, 0.53 to 0.94) and specificity ranged from 0.77 to 0.87 (95% CI range, 0.71 to 0.94) (k=3).

Longer, Self-Administered Instruments (>10 Minutes)

The test accuracy of four longer, self-administered tests was reported in eight studies (n=2,271) (**Table 6; Figure 8**). The tests were the CAMCI (k=1), CAST (k=1), CIDS/SCIDS (k=1), and IQCODE/IQCODE-Short (k=5).

The most common instruments evaluated were the full 26-item IQCODE and the 12-item IQCODE-Short. To screen for dementia, sensitivity ranged from 0.80 to 0.83 (95% CI range, 0.55 to 0.97) and specificity ranged from 0.51 to 0.91 (95% CI range, 0.46 to 0.94) (k=4). For detection of cognitive impairment, sensitivity ranged from 0.71 to 0.82 (95% CI range, 0.54 to 0.87) and specificity ranged from 0.69 to 0.92 (95% CI range, 0.63 to 0.95) (k=3). The other three tests were reported in only one study each and reported sensitivity of 0.83 or higher and specificity of 0.87 or higher to detect dementia or cognitive impairment.

Key Question 3. What Are the Harms of Screening for Cognitive Impairment in Community-Dwelling Older Adults?

We found no studies that directly addressed potential 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). Based on the test accuracy studies included for KQ 2 where most very brief tests had a sensitivity of 75 percent or higher and a specificity of 80 percent or higher, very brief tests could result in up to 20 percent false positives and 25 percent false negatives among older adults screened for dementia. The brief tests performed somewhat better and would likely yield fewer false positives and false negatives; for example, the pooled MMSE resulted in 89 percent sensitivity and 90 percent specificity, which yields approximately 10 percent for both false positives and false negatives.

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

We identified 224 trials representing over 50,000 patients and/or caregivers and three cohort studies with over 190,000 patients that addressed the treatment or management of MCI or mild to moderate dementia (**Table 7; Appendix C**). Forty-eight trials plus three observational studies addressed the benefits and harms of AChEIs and memantine, 29 trials addressed other medications and supplements, 61 trials addressed nonpharmacologic patient-level interventions, and 88 trials addressed caregiver and caregiver-patient dyad interventions (**Table 8**). Just over one-third of this evidence (82/224 studies) was newly identified, with most new evidence related to nonpharmacologic patient-level interventions and caregiver interventions. We discuss the benefits and harms of each type of intervention separately due to the broad range of interventions we examined.

Overall, based on 48 trials (n=22,431) that evaluated **AChEIs** (i.e., donepezil [k=18;n=6,209], galantamine [k=10; n=7,464], rivastigmine [k=8; n=4,569]) and **memantine** (k=12; n=4,189), these medications may improve measures of global cognitive function in the short term, but the magnitude of change is small. In meta-analyses, the differences in changes between those on AChEIs or memantine compared with those on placebo ranged from approximately 1 to 2.5 points on the ADAS-Cog-11 (scale range 0-70) and 0.5 to 1 point on the MMSE (scale range 0-30) over 3 months to 3 years of followup (**Table 9**). There was no clear pattern of effects across outcomes that suggested greater benefit of one medication over another. AChEIs and memantine

appeared to increase the likelihood of improving or maintaining patients' global function by 15 percent (for memantine) to 50 percent (for rivastigmine) in the short term (pooled 95% CI range, 0.49 to 2.69); change at longer followup was not reported. Outcome measures of physical function were only reported in about half the trials and showed mixed results. Other important measures such as neuropsychiatric symptoms and rates of institutionalization were rarely reported; no medication trials included measures of QOL. Only eight trials of medications examined outcomes beyond 6 months, and generally found persistent effects that were consistent with outcomes from shorter timeframes.

Most of the available evidence on the effectiveness of FDA-approved medications came from trials involving people with dementia, particularly among those with moderate versus mild forms of dementia, mostly commonly Alzheimer's disease. Four trials (n=1,919) tested these medications in people with MCI; these trials, testing donepezil and memantine, showed no benefit on global cognitive function. The mean age of participants across medication trials was 74 years old. Only one trial reported an outcome of progression of MCI to AD, finding no differences in the rate of conversion between those on donepezil versus placebo at 3 years.

Overall, side effects from these medications were quite common. Adverse events (AEs) were reported in all 48 trials (n=22,431) in addition to 3 large observational studies (n=190,076). Discontinuation was more common with AChEIs than placebo (13% withdrew for donepezil and rivastigmine, 14% for galantamine, and 8% for placebo) (**Table 9**). Total AEs were also statistically significantly higher for all three types of AChEI versus placebo. In trials that tested various doses of medications, there was some evidence of slightly higher total AEs and withdrawals among arms receiving the higher doses than those with a lower dose (i.e., 10mg vs. 5mg donepezil, 32mg vs. 24mg galantamine, and 6-12mg vs. 1-4mg rivastigmine) although no formal tests of differences between these groups were reported. Memantine appeared to be better tolerated (8% withdrew), with no difference in discontinuation rates or total AEs compared with placebo. Overall, there did not appear to be a difference in total serious adverse events (SAEs) for these medications across trials with limited duration of followup. However, individual studies, including observational evidence, reported increased rates of bradycardia, and relatedly, of syncope, falls, and need for pacemaker placement among those exposed versus unexposed to AChEIs.

Twenty-nine trials (n=6,489) evaluated **other medications or supplements**, including antihypertensives, HMG-CoA reductase inhibitors (atorvastatin and simvastatin), NSAIDs (ibuprofen, naproxen, indomethacin, and celecoxib), gonadal steroids (estrogen [plus or minus progesterone] and testosterone), and dietary supplements and vitamins (multivitamins, B vitamins, vitamin E, and omega-3 fatty acids). None of these had any benefit on global cognition or physical function in people with mild to moderate dementia or MCI (mean age=75 years). Twenty-one of the trials (n=5,688) reported on harms with harms not clearly significantly increased in intervention groups compared with control groups.

We identified 61 trials (n=7,847) that evaluated **nonpharmacologic patient-level interventions**, including cognitive-focused, exercise, and multicomponent and other interventions. In general, these trials were quite small and of limited duration. The body of evidence represented both people with dementia and those with MCI, with a mean age of 76 years across trials. Among all

interventions, there was no clear benefit on global or domain-specific measures of cognitive function compared with control conditions at 3 months to 2 years followup among people with MCI or dementia (**Table 9**). Effect estimates generally favored the intervention groups over control groups, but the magnitude of effect was inconsistent across trials and represented very wide CIs (ranging from no effect to a large effect). While a pooled analysis of cognitive training, stimulation, and rehabilitation intervention trials found a small, statistically significant mean difference of 1.33 points on MMSE scores (95% CI, 0.29 to 2.37; k=15) favoring cognitive-focused interventions compared with control conditions at 3 to 12 months followup, there was substantial clinical and statistical heterogeneity given these inconsistencies. Furthermore, combining eight trials that reported change in ADAS-Cog scores found a slightly greater improvement of 0.66 points (scale range 0-70 where higher scores indicate greater cognitive impairment) among intervention vs. control group participants, but this difference was not statistically significant (MD, -0.66 [05% CI, -1.60 to 0.29]. There was no evidence that the effect of the interventions was modified based on study, population, or intervention characteristics and no evidence of longer-term effects (up to 2 years) on cognitive function. Physical function outcomes, including change in ADLs and IADLs, as well as QOL and mental and neuropsychiatric symptoms, were inconsistently reported. Cognitive training, stimulation, and rehabilitation interventions consistently resulted in very little change over time in both intervention and control groups or small and relatively equal decline in these measures from baseline to 3 months to 2 years, and few trials reported any statistically significant benefit. For trials of exercise interventions, pooled, conservative estimates of differences in measures of global cognitive function show no to small effects based on the MMSE (MD, 1.17 [95% CI, 0.45 to 1.90]; k=10, n=1,168) and ADAS-Cog (MD, -1.05 [95% CI, -1.60 to 0.29]; k=8; n=1,071) at 3 to 12 months followup. There was, however, a pattern of effect for exercise interventions, with small improvements seen in measures of physical function and symptoms for intervention groups, whereas control groups reported worsening function. The clinical meaningfulness of these differences, however, and the possibility of selective reporting limit this finding. There was no consistent benefit of multicomponent and other patient-level interventions across outcomes. Little harm was evident in the few (k=12, n=2,370) trials that reported harms.

Finally, we included 88 trials (n=14,880) that evaluated the effect of multiple types of **caregiver or caregiver-patient dyad interventions**. Most of the caregiver and caregiver-patient dyad trials randomized greater than 100 participants or dyads, and almost half of the trials took place in the United States (40/88). These trials followed participants for slightly longer durations than the patient-focused intervention trials, with just about half of the trials following participants for 1 year or longer. Over half of the trials targeted caregivers only, while the remaining targeted both the patient and caregiver or the entire family. Almost all included evidence pertained to patients (or their caregivers) with dementia; very few had evidence pertaining to patients with MCI. Also, most trials represented patients with moderate as opposed to mild dementia with a mean age across trials of 78 years.

Overall, there was a consistent benefit of psychoeducation and care and case management interventions on caregiver burden and depression outcomes (**Table 9**). Effect sizes were mostly small, however, and were of unclear clinical significance. Psychoeducation interventions resulted in a small but statistically significant benefit on caregiver burden at 3 to 12 months (standardized mean difference [SMD], -0.24 [95% CI, -0.36 to -0.13]; k=27; n=2,776; I^2=50.2%) and a

medium effect on caregiver burden was seen for care and case management interventions (SMD, -0.54 [95% CI, -0.85 to -0.22]; k=8; n=1,215; I^2=82.9%). The clinical importance of these changes in self-reported caregiver burden scores is unclear, however, with these standardized effects translating to a between-group difference of approximately 2 to 4 points on the Zarit-22 (scale range 0-88), the equivalent of changing from being bothered "always" to "sometimes" or "almost never" on 1 or 2 of the 22 items. Similarly, small effect sizes were seen for caregiver depression outcomes. Across both outcomes and across trials, the 95% confidence intervals of the study-level between-group differences were often wide, suggesting a range in benefit (or lack thereof) across participants. There was no evidence in our meta-regressions that one type of intervention (psychoeducation vs. care or case management vs. other caregiver or caregiver-patient dyad interventions) was more effective than the others on measures of caregiver burden or caregiver depression. Likewise, there were no study, population, or intervention characteristics that consistently and robustly predicted larger effects on caregiver burden or depression outcomes.

Other outcomes such as caregiver or patient QOL, rates or time to institutionalization, patient mental health and neuropsychiatric symptoms, and patient functional ability were sparsely reported across the trials with no consistent evidence of a benefit. Decision-making and preparation for meeting dementia-related needs were only reported by one trial each with neither finding statistically significant benefit of the interventions versus control conditions on overall scores for these measures. Only four trials (n=486) reported monitoring harms related to the intervention, and no harms were evident.

Key Question 4. Do Interventions for Mild to Moderate Dementia or Mild Cognitive Impairment in Community-Dwelling Older Adults Improve Decision Making, Patient, Family/Caregiver, or Societal Outcomes?

Key Question 5. What Are the Harms of Interventions for Mild to Moderate Dementia or Mild Cognitive Impairment in Community-Dwelling Older Adults?

Pharmacological Interventions

AChEIs and Memantine

In all, 48 fair- to good-quality RCTs (n=22,431) evaluated the effectiveness and harms of AChEIs or memantine for cognitive impairment. We identified 18 donepezil trials (n=6,209),[184-201] 10 galantamine trials (n=7,464),[202-211] 8 rivastigmine trials (n=4,569)[212-219] and 12 memantine trials (n=4,189).[220-231] Six trials are new, including one on donepezil,[189] one on galantamine,[205] and four on memantine.[221, 222, 224, 227] Three additional, large observational studies (n=190,076), including one new study, evaluated harms related to AChEIs.[232-234]

The primary effectiveness outcomes for trials of pharmacologic interventions were measures of global cognitive function and global function (often referred to as overall dementia severity). The ADAS-Cog-11 and MMSE were the most commonly used instruments for assessing global cognitive function. The ADAS-Cog-11 consists of 11 parts including a word recall task, naming objects and fingers, following commands, constructional praxis, ideational praxis, orientation, word recognition task, remembering test directions, spoken language, comprehension, and word-finding difficulty. The total score ranges from 0-70 and captures the errors for each task; the greater the cognitive impairment, the greater the score. The MMSE combines scores from the five cognitive domains of orientation (10 points), memory (3 points for registration and 3 points for recall), attention/calculation (5 points), language (8 points), and visuospatial abilities (1 point) for a total score ranging from 0-30 where lower scores indicate greater cognitive impairment. Global function was almost exclusively reported as a measure of the clinician's impression of change, typically assessed with the CIBIC+. The CIBIC+ is a comprehensive global measure of detectable change in cognition, function, and behavior based on separate interviews with the patient and an informant. Clinicians assess any change in the patients' condition from baseline with a score ranging from 1 to 7, where 1=very much improved, 4=no change, and 7=very much worse. Other measures of global function such as the Global Deterioration Scale (a clinician's rating based on cognitive change only) were less commonly used. Less than half of the trials of pharmacotherapy reported the effects of the medications on patients' physical function and mental or neuropsychiatric symptoms and no studies reported the effects on QOL. Harms related outcomes were reported by all the included trials.

Study, population, and intervention characteristics of all included studies are presented in **Table 10** and **Table 11**. A summary of results is provided in **Table 12** and detailed results for each outcome are provided in **Appendix E**.

Donepezil

Study and Population Characteristics

Eighteen fair- to good-quality trials involving 6,209 participants evaluated the effectiveness of donepezil for cognitive impairment. Eleven studies (61%) recruited patients partially or fully from the United States. Studies lasted a median of 6 months, with a range of 3 to 36 months. Fifteen studies evaluated donepezil for dementia, while three evaluated donepezil for MCI. The mean baseline MMSE for participants was 22.0, and 52 percent of study participants were women. Most donepezil trials enrolled participants with AD (k=11, n=2,827), but two trials enrolled participants with VaD (n=1,219),[184, 200] two trials enrolled participants with LBD (n=282),[189, 193] and three trials enrolled participants with MCI (n=1,881).[186, 194, 197] Only one donepezil study was published since the last review – a study of 142 participants with LBD.[189] Only seven studies reported on race, and these described overwhelmingly white samples: 87 percent in one study and 92 to 100 percent in the others. Only two studies reported on education, with one study reporting a mean of 15 years of education for the sample,[197] and the other study reporting that 53 percent of the sample had 8 to 15 years of education and 47 percent had more than 15 years of education.[186]

Intervention Characteristics

The daily dosage of donepezil ranged from 1 to 10 mg, with all trials using 5 to 10 mg per day in at least one trial arm. Most studies started participants on doses of 5 mg per day, increasing to 10 mg per day after 2 to 6 weeks. All control participants were given placebo.

Results

Cognitive function. Differences in global cognitive function favoring donepezil were statistically significant, but generally small and of unclear clinical significance. Fourteen of the 18 studies had sufficient data to meta-analyze cognitive function results using the ADAS-Cog or the MMSE. For ADAS-Cog scores, the pooled between-group mean difference in change was 2.13 points in favor of the intervention group (95% CI, -3.32 to -0.94; k=6; n=1,981; I^2=64.4%) (**Figure 9**), usually from an improvement in the intervention group of 1 to 4 points and no change or a decline in the placebo group of up to 4 points. Most studies reported differences at 6 months. Only one study followed participants for more than 12 months;[194] the difference in ADAS-Cog scores for the group treated with donepezil and the group on placebo gradually decreased in magnitude between 6 months and 36 months, but the difference was not statistically significant at any time. Consistent with the findings from the meta-analysis, two studies reported a higher percentage of patients treated with donepezil compared to the placebo group improving by 4 points or more on the ADAS-Cog 13 (37% versus 16% [p=0.02][198] and 50% versus 32% [p-value not reported][197]). For MMSE scores, the pooled between-group mean difference in change over 3 to 36 months was 1.24 points (95% CI, 0.81 to 1.67; k=12; n=3,192; I^2=65.3%,) (**Figure 10**), usually from no change or an improvement of up to 2 points in those on donepezil and no change or a decline of up to 3 points in those on placebo. In the one study that reported longer followup the MMSE score of both the group treated with donepezil and the group on placebo declined over time and the magnitude and direction of the difference between the two groups remained consistent and not statistically significant.[194] The Egger's test of bias was statistically significant (p=0.015) for results for the MMSE indicating a small studies effect, which is a marker of potential publication bias. Due to this potential bias, the pooled estimate may overestimate the true effect.

Findings were similar for all types of cognitive impairment, including AD, LBD, VaD, and MCI. Six donepezil studies reported outcomes on at least one specific cognitive domain. There was no evidence of significant differences in language or memory between participants exposed to donepezil compared with those exposed to placebo, while results were mixed regarding differences in attention or executive functioning between groups.

Global function. Thirteen of the 18 donepezil trials reported global function using measures such as the CIBIC+ or the Clinical Dementia Rating Scale Sum of Boxes. Most trials reported a benefit of donepezil as compared with placebo. In a pooled analysis, participants taking donepezil had a 31 percent higher likelihood of improving or maintaining their global function at 3 to 12 months compared with those on placebo (RR, 1.31 [95% CI, 1.12 to 1.53]; k=9; n=2,440; I^2=77.4%) (**Figure 11**). Likewise, when looking at continuous measures of global function, there was a small, statistically significant association between donepezil and higher global function at 3 to 11 months (SMD, -0.24 [95% CI, -0.39 to -0.09]; k=8; n=3,302; I^2=70.7%) (**Figure 12**).

Physical function. Only 7 of 18 donepezil trials reported a measure of physical function. Studies used a wide variety of instruments to measure ADLs or IADLs or a combination of these; only two studies used the same instrument (the ADFACS). Four of these trials reported a statistically significant difference in favor of those randomized to donepezil. While the remaining three trials did not report a statistically significant difference, their results favored the intervention in that they declined less than those on placebo or improved at followup. However, these changes were very small; for example, an improvement of 1–2 points on a scale from 0-100.

Neuropsychiatric symptoms. Six donepezil studies evaluated behavioral and neuropsychiatric symptoms in their trials using the 10- or 12-item Neuropsychiatric Inventory, with mixed findings. Three studies found significant differences in behavioral and neuropsychiatric symptoms between donepezil and placebo groups at 3 to 6 months[187, 188, 193] whereas the other three studies did not find such differences over 3 to 11 months.[186, 189, 199] Of note, in one study of 140 patients with LBD, differences in the Neuropsychiatric Inventory that favored the intervention were seen in those exposed to 5 and to 10 mg of donepezil per day but not those exposed to 3 mg per day.[193]

Other outcomes. A 3-year study of 769 people with MCI that investigated both donepezil and vitamin E reported progression to AD.[194] While donepezil was associated with a lower rate of progression from MCI to AD at the end of years 1 (HR=0.42 [95% CI, 0.24 to 0.76]) and 2 (HR=0.64 [95% CI, 0.44 to 0.95]), the rate of progression from MCI to AD at 3 years was not different between donepezil and placebo groups (HR=0.80 [95% CI, 0.57 to 1.13]). Three studies showed a decrease in caregiver burden (two as measured by the Zarit-22).[188, 189, 193] This decrease, however, was not always statistically significant and often small (change from baseline ranging from an improvement of 5 points to a decline of 1 point for the caregivers in the group treated with donepezil and from no improvement to a decline of 4 points for caregivers in the control group). Other outcomes, including QOL and rates of institutionalization, were not reported in trials of donepezil. While many of these studies reported mortality as part of their patient tracking throughout the trial, these studies were not designed or powered to detect mortality differences between groups.

Harms. All 18 trials and one observational study reported potential harms of donepezil. Total AEs were statistically significantly higher in the group receiving donepezil (84%) versus the control group (76%) with a pooled RR of 1.10 (95% CI, 1.06 to 1.13; k=12; n=3,212; I^2=0%) (figure not shown). The most commonly reported adverse events with donepezil were diarrhea and nausea. SAEs were not statistically significantly different between intervention (12%) and control groups (10%) in our meta-analysis (RR, 1.18, [95% CI, 0.99 to 1.40]; k=12; n=4,045; I^2=0%) (**Figure 13**), although results of individual trials were mixed with some suggesting up to a 70 percent greater risk of SAEs in control participants and others reporting up to an 80 percent greater risk among those on donepezil. Furthermore, individual studies reported increased rates of bradycardia, and, relatedly, of syncope, falls and need for pacemaker placement.[232, 233] Study withdrawals due to adverse events were statistically significantly higher in patients receiving donepezil (13%) than in patients receiving placebo (8%) (RR, 1.88 [95% CI, 1.54 to 2.29]; k=13; n=4,124; I^2=8.8%) (**Figure 14**).

Galantamine

Study and Population Characteristics

Ten fair- to good-quality trials enrolling 7,464 participants assessed the effectiveness of galantamine for cognitive impairment. Only one galantamine study—of 2,045 participants with AD—was published after the last review.[205] Five studies (50%) recruited patients in part or fully from the United States. Trials were conducted for 3 to 12 months, with a median of 6 months. All galantamine studies recruited patients with dementia; most studies (k=8; n=6,084) enrolled patients with AD, while one study enrolled patients with VaD (n=788)[202] and one study enrolled patients with AD (48%), VaD (43%), or other dementias (9%) (n=592).[204] None of the trials of galantamine included patients with MCI. The mean baseline MMSE score was 19.1, and 59 percent of participants were women. Six studies reported race, with white participants accounting for 91 to 100 percent of the sample. Only one galantamine study characterized the education level of the sample; it reported a mean education of 11 years.[207]

Intervention Characteristics

The daily dosage of galantamine ranged from 8 to 36 mg, with most trials giving 16 to 24 mg per day. Studies generally titrated doses weekly to monthly until the target dose was reached. All control participants were given placebo.

Results

Cognitive function. All 10 studies of galantamine reported the effect of the medication on global cognitive function, using the ADAS-Cog or the MMSE. The pooled between-group mean differences in change in the ADAS-Cog score was 2.13 points in favor of those randomized to receive galantamine (MD, -2.13; 95% CI, -2.94 to -1.32; k=9; n=3,786; I^2=65.9%) over 3 to 6 months **(Figure 9**). Four studies[204, 208-210] reported a higher percentage of patients treated with galantamine compared to the placebo group improving by 4 points or more on the ADAS-Cog 11 (difference in proportion improving between groups ranging from 12 to 17 percent, with three studies reporting statistically significant differences). Only one study of 1,765 patients with AD reported MMSE findings,[205] with a mean between-group difference of 0.58 points (95% CI, 0.26 to 0.90) over 12 months (**Figure 10**). There was no apparent difference in the effectiveness of galantamine among those with AD versus VaD.

Global function. Nine of the 10 galantamine studies reported a global function outcome. Eight of these reported global function outcomes using the CIBIC+ dichotomized according to the number of patients whose global function was maintained or improved versus those whose global function declined over time. The relative risk indicated a 21 percent higher likelihood of improvement or maintenance in global functioning among those on galantamine versus placebo at 3 to 6 months (RR, 1.21 [95% CI, 1.11 to 1.31]; k=8; n=3,486; I^2=56.2%) (**Figure 11**). Five studies reported global function using the CIBIC+ on a continuous scale. In all studies, those on galantamine had higher global function scores (5.3) versus those on placebo (5.1), and two of these trials found that difference to be statistically significantly different.[207, 210]

Physical function. All but one trial of galantamine reported a measure of ADLs or IADLs. Six of the trials demonstrated a benefit in physical function for at least some subgroups taking galantamine at doses of 16 to 32 mg per day compared with those taking placebo. Various instruments and scales were used, so the magnitude of the differences is hard to compare. In most cases, the differences between groups were small, ranging from about 1 to 4 points.

Neuropsychiatric symptoms. Four trials of galantamine evaluated behavioral and neuropsychiatric symptoms using the 10- or 12-item Neuropsychiatric Inventory. Findings were mixed. Two studies reported significant differences favoring galantamine in behavioral and neuropsychiatric symptoms for those taking 14 to 24 mg of galantamine per day compared with those taking placebo at 5 or 6 months.[204, 209] In contrast, there were no such differences in two studies of 8 to 32 mg of galantamine per day at 3 to 6 months.[203, 208] Of note, one study of 978 patients with AD found differences in the 10-item Neuropsychiatric Inventory at 5 months that favored galantamine at doses of 16 to 24 mg per day, but not at doses of 8 mg per day.[209]

Other outcomes. None of the trials of galantamine reported QOL measures or rates of institutionalization. One study examined caregiver burden using the NPI-10 and found no difference between groups. Only one trial carefully ascertained mortality and was intended to determine whether there was mortality benefit from galantamine treatment.[205] This study reported a HR of 0.58 (95% CI, 0.37 to 0.89; p=0.011), indicating that patients treated with galantamine had a higher survival rate than those treated with placebo. The remaining studies reported mortality as part of their patient tracking and were not designed or powered to detect mortality differences between groups.

Harms. All 10 trials of galantamine reported harms. Total AEs were statistically significantly higher for those receiving galantamine treatment (73%) compared with the control group (63%) (RR, 1.14 [95% CI, 1.06 to 1.22]; k=9; n=6,004; I^2=57.7%) (figure not shown). Eight of nine trials and one observational study reported SAEs with galantamine. Rates of SAEs were similar in those treated with galantamine (12%) versus those taking placebo (11%) (RR, 1.06 [95% CI, 0.91 to 1.24]; k=7; n=4,987; I^2=97.8%) (**Figure 13**). However, study withdrawals due to adverse events were statistically significantly higher in patients taking galantamine (14%) than in those taking placebo (7%) (RR, 1.98 [95% CI, 1.52 to 2.57]; k=10; n=6,147; I^2=51.1%) (**Figure 14**).

Rivastigmine

Study and Population Characteristics

Eight fair- to good-quality trials involving 4,569 participants evaluated the effectiveness of rivastigmine for cognitive impairment, none published since the previous review. Four studies (50%) recruited patients partially or fully from the United States. Trials ran for a median of 6 months, with a range from 3 to 6 months. All studies evaluated rivastigmine for dementia, and none enrolled participants with MCI. Five studies enrolled participants with AD (n=3,699),[212, 214, 215, 218, 219] two studies enrolled participants with VaD (n=750),[213, 217] and one study enrolled participants with LBD (n=120).[216] Four studies reported on race; white participants ranged from 75 to 97 percent. Three studies reported mean years of education of 3.3 years, 9.3 years, and 9.9 years.[213, 217, 219]

Intervention Characteristics

The daily dosage of rivastigmine ranged from 1 to 17 mg, with considerable variability in daily dosage. Timing of dose escalation also varied between studies, with dose changes usually occurring weekly or monthly. All eight trials delivered rivastigmine orally; one of these trials also included two groups randomized to a rivastigmine patch (9.5 mg or 17.4 mg per day).[219] All control participants in all studies of rivastigmine were given placebo.

Results

Cognitive function. Differences in cognitive function favored rivastigmine over placebo at 3 to 6 months, although most differences were small. The pooled between-group mean difference in change in ADAS-Cog score favored rivastigmine by 2.43 points (MD: -2.43; 95% CI, -0.75 to -4.10; k=5; n=2,618; I^2=81.9%) over 3 to 6 months (**Figure 9**). Two studies[215, 218] reported a higher percentage of patients treated with rivastigmine compared to the placebo group improving by 4 points or more on the ADAS-Cog 11 (difference of 9 or 10% between groups, $p<0.05$ for both studies). The pooled between-group mean difference in change in MMSE score favoring rivastigmine was 0.88 points (95% CI, 0.28 to 1.49; k=6; n=2,415; I^2=44.9%) (**Figure 10**). These findings held across dementia diagnoses, including AD and VaD.

Global function. Seven of eight rivastigmine studies reported global function and had sufficient data for a meta-analysis. In the five studies that presented dichotomous measures of global functioning (i.e., improved or maintained versus declined), the relative risk indicated a 50 percent higher likelihood of improvement or maintenance in global functioning for those on rivastigmine compared with those on placebo at 3 to 6 months (RR, 1.50 [95% CI, 1.22 to 1.85]; k=5; n=1,934; I^2=61.4%) (**Figure 11**). In the six studies that presented continuous measures of global function, meta-analysis of the SMD did not find an association between rivastigmine and global function at 6 months (SMD, -0.14 [95% CI, -0.36 to 0.08]; k=6; n=2,535; I^2=85.7%) (**Figure 12**). All studies using the CIBIC+, however, demonstrated an improvement or less of a decline in global function (3 of 4 were statistically significantly different).

Physical function. Seven of eight rivastigmine trials reported physical function outcomes. Four trials found a benefit of rivastigmine at doses of 6 to 17.4 mg per day over 3 to 6 months, with between-group mean differences in change ranging from 1.80 to 3.40 points.[214, 215, 218, 219] Two studies also examined a dichotomous version of the Progressive Deterioration Scale and found a statistically significant difference in groups in favor of the group taking rivastigmine.[214, 218] Two studies found that doses of 1 to 4 mg per day of rivastigmine were not associated with differences in physical function outcomes, while doses of 6 to 12 mg per day were.[214, 218]

Neuropsychiatric symptoms. Four of eight rivastigmine studies evaluated behavioral and neuropsychiatric symptoms in their trials using the 10- and 12-item versions of the Neuropsychiatric Inventory, with mixed results. One study found differences in behavioral and neuropsychiatric symptoms that favored rivastigmine at a dose of 12 mg per day compared with placebo at 5 months.[216] However, the other three studies that reported such outcomes did not find differences between participants taking 3 to 17.4 mg of rivastigmine per day over 6 months compared with those taking placebo.[213, 217, 219] One study examined the effect of rivastigmine on

anxiety symptoms and found no statistically significant difference between the group taking rivastigmine and the group given placebo.[217]

Other outcomes. No rivastigmine studies reported on QOL measures or rates of institutionalization. While many of the studies reported mortality as part of their patient tracking throughout the trial, they were not designed or powered to detect mortality differences between groups.

Harms. All eight trials of rivastigmine plus one observational study reported AEs. Total AEs were statistically significantly higher among patients treated with rivastigmine (90%) versus those on placebo (73%) (RR, 1.23 [95% CI, 1.12 to 1.35]; k=4; n=1,090; I^2=0%) (figure not shown). While SAE rates were not significantly different between those receiving rivastigmine (14%) and those receiving placebo (12%) (RR, 1.15 [95% CI, 0.92 to 1.43]; k=6; n=2,619; I^2=10.4%) (**Figure 13**), the results for individual studies were mixed, ranging from a 300 percent greater risk from rivastigmine to a 20 percent greater risk from placebo. Nevertheless, study withdrawals due to AEs were higher in those taking rivastigmine (13%) compared with those taking placebo (6%) (RR, 2.21 [95% CI, 1.54 to 3.17]; k=8; n=3,131; I^2=57.0%) (**Figure 14**).

Memantine

Study and Population Characteristics

Twelve trials of fair-to-good quality, including four new trials, involving 4,189 participants examined memantine for cognitive impairment. Four studies (33%) recruited patients partially or fully from the United States. Trials were conducted for a median of 6 months and a range of 3 to 48 months. Eleven studies recruited people with dementia, with nine studies recruiting people with AD (n=3,229)[220-222, 224, 226-229, 231] and two studies recruiting people with VaD (n=900).[225, 230] One study recruited people with MCI (n=60).[223] The mean baseline MMSE score was 17.8, a bit lower than the trials of AChEIs, which is to be expected of a medication that has an FDA indication for moderate to severe AD. Women comprised 49 percent of memantine trial samples. Four studies were published after the last review, all of which recruited participants with AD (n=1,380).[221, 222, 224, 227] Seven studies reported race and one reported ethnicity data; white participants comprised 86 to 100 percent of samples, while Hispanic ethnicity comprised 11 percent of one sample. Two memantine trials reported education, with one study reporting that 78 percent of participants had at least a high school education[222] and another reporting a mean education of 11.5 years for participants.[229]

Intervention Characteristics

All trials of memantine used an oral daily dosage of 20 mg, most often achieved by titrating from a starting dose of 5 mg per day and increasing the dose weekly by 5 mg per day. Two studies required all participants (those in intervention and control groups) to be on the rivastigmine patch at 9.5 mg per day[221] or galantamine at 24 mg per day.[227] All trials were placebo-controlled, with the exception of one open-label study in which intervention participants received both memantine and rivastigmine and control participants received rivastigmine only (and no placebo).[221]

Results

Cognitive function. Differences in cognitive function with memantine were generally statistically significant for participants with cognitive impairment. Nine of 12 memantine trials had sufficient data to meta-analyze cognitive function results using the ADAS-Cog or the MMSE. The pooled between-group mean difference in change in ADAS-Cog score was small, but statistically significantly different (MD, -0.88 [95% CI, -0.11 to -1.65]; k=8; n=2,609; I^2=78.1%) (**Figure 9**) whereas the pooled between-group mean difference in change in MMSE score was not (MD, 0.36 [95% CI, -0.31 to 1.04]; k=5; n=1,217; I^2=33.2%) (**Figure 10**). One study had longer-term followup (4 years) and found no difference between the group given memantine and the group given placebo for cognitive function.[222] Findings were clinically marginal regardless of type of cognitive impairment, including AD, VaD, and MCI.

Global function. A smaller proportion of memantine trials reported global function outcomes compared with trials of AChEIs. While the pooled analysis of five trials (n=1,396) reporting results for the CIBIC+ using the random effects model resulted in a small association between memantine and global function favoring memantine (SMD in change, -0.14 [95% CI, -0.27 to -0.01]; k=5; n=1,396; I^2=32.9%), this result was sensitive to the use of a REML model correcting for small samples, resulting in a more conservative and no longer statistically significant association (MD in change, -0.14, 95% CI: -0.33 to 0.05, I^2=32.9%) (**Figure 12**). Consistent with the continuous results, two studies reported a dichotomous measure of global function in favor of those on memantine; but this association was not statically significant after using the more conservative REML model (RR 1.15 [95% CI, 0.49 to 2.69]; k=2; n=545) (**Figure 11**).

Physical function. Six of 12 memantine trials reported physical function outcomes. Only one study found statistically significant differences in physical function at 4 and 6 months (but not at 12 months) favoring memantine, but these differences were small in magnitude (between-group mean difference in change at 4 months: 0.48 (95% CI, 0.19 to 0.77) and at 6 months: 0.85 (95% CI, 0.51 to 1.19).[227] The other five trials found no differences in physical function in those exposed and unexposed to memantine. Additionally, only one study had longer-term followup (4 years) and found no difference between the group given memantine and the group given placebo for physical function.[222]

Neuropsychiatric outcomes. Eight memantine trials reported on behavioral and neuropsychiatric symptoms using the 12-item Neuropsychiatric Inventory. Findings were mixed with some trials showing improved scores among those taking memantine and worse scores among those on placebo whereas others reported the opposite (improvement among those on placebo, and not memantine), and only one trial reported a statistically significant benefit of memantine at 3 and 6 months.[226] The one trial reporting longer term outcomes found no difference at 4 years.[222]

Other outcomes. One study reported on institutionalization and found a lower rate of nursing home placement in those taking memantine (2/182) compared with those taking placebo (9/187) at 6 months.[224] None of the trials reported measures of QOL. One study conducted a survival analysis and found no statistically significant difference in mortality between memantine and placebo groups over 4 years (HR 1.06; 95% CI, 0.91 to 1.24).[222]

Harms. All 12 trials of memantine reported on harms. Total AE rates were similar between those taking memantine (65%) and those taking placebo (62%) (RR, 1.04 [95% CI, 0.99 to 1.09]; k=11; n=3414; I^2=0%). Rates of SAEs for individual trials were mixed, with some suggesting as much as a 71 percent greater risk of SAEs in control participants and others reporting up to a 68 percent greater risk among those on memantine. Across studies, however, rates of SAEs were not different between intervention and control groups (RR, 0.88 [95% CI, 0.77 to 1.01]; k=10; n=3,350; I^2=0%) (**Figure 13**). Likewise, and in contrast to the AChEIs, withdrawals due to AEs were not significantly different between patients receiving memantine (8%) and those receiving placebo (7%) (RR, 1.26 [95% CI, 0.98 to 1.62]; k=9; n=3,288; I^2=0%) (**Figure 14**).

Other Medications and Supplements

We included 29 trials (n=6,489) that examined the benefits and/or harms of using other medications or supplements for cognitive impairment. Twenty-four of these studies were included in the previous review, while five were newly identified for this update. A variety of different medications and supplements were evaluated, including antihypertensives (k=1, n=385),[235] 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (also known as statins; k=4, n=1,153),[236-239] nonsteroidal anti-inflammatory drugs (NSAIDS; k=4, n=837),[240-243] gonadal steroids (k=6, n=337),[244-249] and dietary supplements such as vitamins or omega-3 fatty acids (k=14, n=3,777).[194, 222, 250-261]

In general, the primary effectiveness outcomes for these trials were measures of global cognitive function, most often the ADAS-Cog-11 or MMSE. In some trials, however, global cognitive function was a secondary outcome whereas measures of physical function or domain-specific cognitive function, for example, were primary outcomes. Fewer than half of the studies reported a measure of global function. Of those that did, most (9 out of 12 studies) used the CIBIC+; the remaining studies used the CDR-SB and CDR alone or in addition to the CIBIC+. Patient mental and neuropsychiatric symptoms were measured in two-thirds of the trials, typically depression symptoms with a variety of instruments or composite neuropsychiatric symptoms with the NPI-12. A little over half of the studies reported the effect of medications or supplements on physical function and few trials reported a measure of QOL. Harms related outcomes were reported by 20 of the 29 the included trials.

Study, population, and intervention characteristics of all 29 trials are presented in **Table 13** and **Table 14**. A summary of results for all included trials is provided in **Table 15**, while detailed results related to global function, global cognitive function, physical function, neuropsychiatric symptoms, and harms are presented in **Appendix F**.

Antihypertensives

We identified one new study on the effects of discontinuing antihypertensives among participants with cognitive impairment.[235] For 385 participants with MCI who were randomized to discontinue or continue their antihypertensive medication, there were no differences between groups in global cognitive function, executive function, memory, physical function, depressive symptoms, or QOL at 4 months. Similarly, no differences in rates of serious adverse events,

including death, hospitalizations, or vascular events, were seen between those continuing (7.0%) or discontinuing (6.5%) their antihypertensives (p-value not reported).

HMG-CoA Reductase Inhibitors

In the four studies (n=1,153) that examined the effects of statins (atorvastatin [k=2] and simvastin [k=2]) for patients with AD dementia, none found differences between intervention and control groups on reported outcomes of global function, global cognitive function, or physical function at 6 to 18 months.[236-239] One trial (n=63) of three examining neuropsychiatric symptoms found a difference in depression symptoms that favored the intervention of atorvastatin at 80 mg per day at 12 months,[239] while the other two found no difference.[236, 237] None of these three studies found a difference in total neuropsychiatric symptom scores between intervention and control groups.

Two HMG-CoA studies reported harms, with no significant differences in total or serious AEs between the intervention and control groups. While neither study found a difference in mortality rates between groups, they were neither designed nor powered to detect a difference in mortality between the intervention and control.

NSAIDs

None of the four studies of NSAIDs (n=837) (celecoxib 40 mg, ibuprofen 800 mg, indomethacin 100 mg, or naproxen 220 mg daily) found differences between intervention and control groups on reported outcomes of global function, global cognitive function, physical function, neuropsychiatric symptoms, QOL, institutionalization, or caregiver burden at 6 to 12 months in participants with AD dementia.[241-243, 250]

All four studies of NSAIDs reported on harms. One trial reporting total AEs found that 229/285 participants (80%) in the intervention and 105/140 participants (75%) in the control group experienced at least one AE, with "generally no significant differences in AEs between groups."[243] Two trials reported no statistically significant difference in SAEs: in one trial, 32/140 participants (23%) in the intervention and 73/285 participants (26%) in the control group experienced a SAE,[243] whereas in the other smaller trial, 5/26 participants (19%) in the intervention group and 1/25 participants (4%) in the control group reported a SAE.[241] None of the four trials reported a statistically significant difference in withdrawals due to AEs. These studies were not designed nor powered to detect a difference in mortality between groups.

Gonadal Steroids

Six studies (n=337), including one new trial, examined the effects of gonadal steroids on patients with dementia, including five studies of estrogen[244, 245, 247-249] (one of which also used progestin[248]) and one study of testosterone.[246] Daily doses of estrogen for women included 0.625 mg to 1.25 mg of estradiol or conjugated equine estrogens (Premarin) or 120 mg of raloxifene, while daily doses of progesterone for women were 0.5 mg daily; daily doses of transdermal or topical testosterone for men were 75 mg daily. No studies of gonadal steroids showed differences in reported outcomes that favored the intervention, including global function, global cognitive function, domain-specific cognitive function, physical function, neuropsychiatric symptoms,

caregiver burden, or QOL. However, two studies of estrogen or estrogen plus progestin found differences in global function at 1 year that favored the control group.[247, 248]

Only two of the six trials reported AEs with both finding greater AEs among those on the study medication versus placebo.[244, 248] One of the studies, however, found more SAEs reported in participants receiving placebo (3 events/32 participants [9.4%] than in those receiving estrogen plus progestin (0 events/33 participants [0%]; p-value not reported).[248] However, these studies were small and in some cases, events were rare. While four of the studies on gonadal steroids reported mortality,[244, 247-249] they were not powered nor designed to detect differences in mortality between groups.

Dietary Supplements

B vitamins. Four studies (n=877) evaluated the efficacy and safety of B vitamin supplementation in the treatment of dementia.[250-252, 254] Specific supplementation included folic acid,[251] folic acid plus vitamins B_6 and B_{12},[250, 252] and folic acid plus B_{12}.[254] One trial[250] required participants to have normal folic acid, B_{12}, and homocysteine levels to be eligible to participate. The other three trials did not restrict inclusion based on baseline homocysteine levels (although no participants were found to have deficiencies) and conducted subanalyses among those with high versus low baseline levels. One 6-month study of 57 individuals with AD who were on AchEIs found that randomization to folic acid was associated with a difference in change from baseline in a combined measure of IADLs and social behavior favoring the intervention at 6 months.[251] There were no differences in global cognitive function or attention between groups and no significant differences between those with high versus normal baseline homocysteine levels. Another larger study of 271 participants with MCI found differences in executive functioning that favored those taking B vitamins compared with those on placebo at 24 months, but found no differences in language, memory, or depression.[252] In subanalyses, there were differences in global cognition and memory favoring the intervention for patients with baseline homocysteine levels above the median. In the remaining two studies, there were no differences in global function, global cognitive function, domain-specific cognitive function, physical function, or neuropsychiatric symptoms for patients with dementia who were or were not exposed to B vitamins.[250, 254]

In two of four studies reporting harms, there were no differences between intervention and control groups in total AEs and SAEs.[250, 252] One study reported mortality but was not designed or powered to detect a difference in mortality between groups.[250]

Vitamin E. Three trials, one of which we identified in this update, reported on the effects of vitamin E for cognitive impairment (n=1551).[194, 222, 257] One new parallel group RCT randomized 613 patients with dementia to memantine, vitamin E (alpha tocopherol), or combination memantine plus vitamin E, or placebo, and found differences in ADLs and IADLs that favored vitamin E at 48 months, but no differences in global cognitive functioning or neuropsychiatric symptoms.[222] Two other vitamin E studies, one in patients with dementia and another in patients with MCI who were also on a multivitamin, did not find differences in reported outcomes of global function, global cognitive function, executive function, language, memory, physical function, neuropsychiatric symptoms, or rates of institutionalization between intervention and control groups at 24 to 36 months.[194, 257]

The two vitamin E studies that reported AE rates found no differences between intervention and control groups.[194, 222] In the longer-term trial of memantine, vitamin E, combination memantine and vitamin E versus placebo, there were no differences in rates of SAEs comparing vitamin E alone versus placebo whereas those on memantine alone or combined memantine and vitamin E did experience greater frequencies of SAEs.[222] This same study conducted a survival analysis and found no statistically significant difference in survival between vitamin E and placebo groups over 48 months (HR 0.87 [95% CI, 0.67 to 1.13]).[222] The remaining two studies were not designed or powered to find differences in mortality rates between intervention and control groups.

Omega-3 fatty acids. Six studies (n=1260), including two new studies, reported on the effects of omega-3 fatty acids on cognition, finding mixed results.[253, 255, 256, 258, 259, 261] One study of 39 patients with dementia found that one formulation of omega-3 fatty acids (DHA 675mg + EPA 975 mg/day) was associated with better IADL scores compared with controls, while another formulation (DHA 675 mg + EPA 975 mg + LA 600 mg/day) was associated with both better IADL scores and better MMSE scores (but not ADAS-Cog scores) compared with controls.[258] Another study of 54 people with MCI found differences in depression outcomes at 6 months that favored the intervention groups, which took one of two formulations of omega-3 fatty acids (DHA 1.95g/day or EPA 1.83g/day), but no differences in attention, language or executive function.[259] Another study of 485 people with MCI randomized to omega-3 fatty acids (DHA 900 mg/day) found differences in executive function at 6 months that favored the intervention, but no differences in global cognitive function, physical function, neuropsychiatric symptoms or caregiver burden.[261] The remaining three studies of omega-3 fatty acids (involving DHA or DHA + EPA) did not demonstrate differences between exposed and unexposed patients with MCI or dementia in global function, global cognitive function, domain-specific cognitive function, physical function, or neuropsychiatric symptoms at 4 to 18 months.[253, 255, 256]

Three of the six omega-3 fatty acids studies reported harms, and none reported differences in rates of total or serious AEs. These studies were not designed or powered to detect differences in deaths between intervention and control groups.

Multivitamins. The lone study of multivitamins (n=89) did not find any effects on reported outcomes of global cognitive function, memory or physical function in 89 participants with dementia at 6 months.[260] There were no differences in rates of adverse events or serious adverse events between groups; deaths were not reported.

Nonpharmacologic Interventions

Patient-Level Nonpharmacologic Interventions

We identified 61 trials (n=7,847) that evaluated nonpharmacologic interventions targeting the patient directly, rather than the caregiver or patient-caregiver dyad. These interventions included: 1) cognitive training, rehabilitation, and/or stimulation (31 arms in 28 trials; n=3,212);[262-289] 2) exercise interventions (21 trials; n=2,831);[290-310] and 3) multicomponent and "other" interventions (16 trials; n=2,302).[278, 289, 307, 310-322] Almost two-thirds of these studies (39 studies) are new to this update; 22 were carried forward from the previous review.

The primary outcome in most patient-level nonpharmacologic interventions was a measure of global- or domain-specific cognitive function. Measures of physical function (ADLs and IADLs) and mental and neuropsychiatric symptoms were reported in approximately half of the trials, with various instruments used. Isolated trials also reported outcome measures related to institutionalization, conversion from MCI to dementia, global function, QOL, or caregiver burden. These results are only mentioned briefly, however, due to the sparse nature of these outcomes and concern of selective reporting.

Given the heterogeneity in interventions, we present results stratified by type of intervention. Study, population, and intervention characteristics for all nonpharmacologic patient-level interventions are presented in **Table 16** and **Table 17**. A summary of results for all included trials is provided in **Table 18**, while detailed results are presented in **Appendix G**.

Cognitive Stimulation, Cognitive Training, and/or Cognitive Rehabilitation

Study and Population Characteristics

Twenty-eight trials (n=3,212) evaluated the effectiveness of cognitive training, stimulation, and/or rehabilitation on improving cognitive or physical function outcomes and mental and behavioral symptoms versus no intervention or an attention control group. Seventeen of the 28 trials were newly identified as part of this update; 11 trials were included in the previous review. We rated only 5 of these trials as good quality and the remaining 22 as fair quality. In general, trials were relatively small (n<100), ranging from 19 to 481 patients randomized (median n randomized = 63). Most were of limited study duration (3 to 6 months followup); only nine trials had followup at 12 months or longer (maximum of 26 months).[265, 266, 274-276, 278, 280, 283, 287]

Eleven of the 28 trials targeted patients with MCI (mean baseline MMSE score ranged from 25.7 to 27.9), 14 targeted patients with dementia (MMSE range, 17.8 to 25.1), and the remaining 2[265, 269] targeted patients with either MCI or dementia (MMSE of 26.4 in one study that reported). Among the trials of patients with dementia, all but two[277, 288] } was exclusively among patients with probable AD. In the remaining trials, most (68% and 83%) had AD, about a tenth had VaD (13% and 7%, respectively), and the remaining diagnoses were PDD or of mixed or other etiology. Most trials recruited patients directly from memory or neurology clinics or some other outpatient clinic. Among the trials targeting patients with MCI, most recruited patients presenting with memory complaints who were free of psychiatric symptoms or disorders. In 4 of the 28 trials,[265, 267, 280, 283] participants were required to be on a stable dose (1 month to 2 years) of an AChEI to be enrolled in the trial whereas five other trials[263, 268, 282, 285, 287] specifically excluded patients who were taking an AChEI or memantine. In the remaining trials, the proportion of participants taking an AChEI at baseline ranged from 32 to 92 percent and was similar across intervention and control groups for each individual study. Across trials, the average age of patients ranged from 68 to 83 years (median=76). These trials included an even distribution of both men and women and were conducted mostly in the United States (k=6) and western Europe (k=13). The race/ethnicity and educational level of participants were rarely reported.

Intervention Characteristics

Thirty-one unique cognitive-focused interventions were tested in the 28 trials. We broadly defined these interventions as those that directly or indirectly targeted cognitive functioning as opposed to those that focused primarily on behavioral, emotional, or physical function.[323] Most of the cognitive-focused interventions were cognitive stimulation interventions (defined as engaging the person with dementia in a range of general activities and discussions aimed at general enhancement of cognitive and social functioning[324]) or cognitive training activities (defined as a guided practice on a set of standardized tasks designed to reflect particular cognitive functions such as memory, attention or problem-solving[323]). Four interventions[264, 272, 275, 276] included individualized cognitive rehabilitation in which personally relevant goals were identified and the interventionist worked with the person and his or her family to devise strategies to address these. In cognitive rehabilitation studies, the emphasis was on improving performance in everyday life rather than on cognitive tests.[323]

Most of the cognitive stimulation and training interventions were group-based interventions, but the intensity of activities varied considerably from 1 day a week for 6 weeks to 5 days a week for up to 2 years (median duration=3 months). Most ranged from 45 to 90 minutes per session. Four interventions tested computer-based cognitive training programs consisting of 24 to 52 sessions total over 2 to 6 months;[278, 281, 284, 285] 3 of these 4 interventions were among patients with MCI. Three interventions were delivered in the home;[270, 273, 274] in two of them caregivers were trained to lead cognitive stimulation or training activities. The few remaining interventions were individual-based, in-person cognitive stimulation or training activities. Across all interventions, the most common interventionists were trained psychologists or neuropsychologists, but others included social workers, occupational and speech therapists, and trained research staff. Where reported, adherence to the interventions was relatively high (e.g., more than 70% of participants completing the full intervention; participants completing 80% of sessions on average).

The comparison groups were highly variable and included no intervention (11 trials with no intervention or waitlist controls), usual care which generally did not include cognitive training (7 trials), brief interventions focused on psychoeducation and support (3 trials), and "sham" cognitive-focused activities (7 trials). In the "sham" control groups, participants took part in non-specific cognitive activities following the same schedule as the intervention group, such as reading the newspaper, completing puzzles, and browsing the Internet, with or without interaction with an interventionist or other participants.

Results

Cognitive function. Twenty of the 28 trials reported results for global cognitive function (e.g., ADAS-Cog, MMSE), with or without reporting domain-specific measures of cognitive function. The remaining eight trials[262, 264, 267, 268, 281, 285, 286, 289] only reported results for domain-specific measures of cognitive function such as memory, executive functioning, or attention. Overall, there appeared to be a very small to no benefit of cognitive training and stimulation activities on global cognitive function at 3 to 12 months (k=21; n=2,754). In 15 trials that reported effects of the intervention on MMSE scores, the pooled result indicated a statistically significant association between cognitive-focused interventions and improved global cognitive function

compared with control groups at 3 to 12 months; however, the confidence interval was quite wide, ranging from a very small to small effect (MD, 1.33 [95% CI, 0.29 to 2.37]; k=15; n=1341) at 3 to 12 months followup. Additionally, there was substantial statistical heterogeneity in the model (I^2=91.1%), which likely reflects the lack of consistency in the magnitude of effects across studies (**Figure 15**). In general, across all trials, the control groups experienced worsening scores on the MMSE from baseline to up to 12 months followup ranging from 0.4 points (-0.4) to 3.6 (-3.6) whereas the effects in the intervention groups were more variable ranging from a decline of 1.3 (-1.3) to an improvement of 3.8 points. Based on the Egger's test and visual inspection of funnel plots, we found no evidence of small-study effects (an indicator of publication bias) for this outcome.

Similarly, a meta-analysis of six trials reporting the differences in change in ADAS-Cog scores between those taking part in a cognitive-focused intervention versus control conditions found a lack of an association with cognitive improvement at 3 to 12 months followup (MD, -0.66 [95% CI, -1.60to 0.29]; k=8; n=842; I^2=0%) (**Figure 16**). The absolute change from baseline in ADAS-Cog scores varied across studies from an improvement of 1.5 points to a drop of 4.9 points in the intervention groups and an improvement of 1.0 points to a decline of 5.6 in the control groups. Again, wide confidence intervals within and between studies reflect clinical uncertainty regarding the magnitude of the effects seen.

Four trials that reported a measure of global cognitive function were not included in either meta-analysis due to data reporting limitations[265, 275] or because they reported a measure other than the ADAS-Cog or MMSE.[270, 276] None of these trials reported a statistically significant effect of cognitive-focused interventions on global function at 3 to 24 months followup, but the direction of effects was consistent with the meta-analyzed trials. There was no evidence that the effect of the intervention was modified based on study quality (good-fair vs. fair), population (dementia vs. MCI), the duration of the intervention, whether the intervention included group sessions or not, or the control group (sham activities vs. other). In the few trials that reported longer-term effects (at greater than 12 months followup),[275, 276, 278] consistent between-group effects were seen over time, with cognitive function declining in both intervention and control group participants.

Eight trials reported results related to measures of specific domains of cognitive function without reporting a measure of global cognitive function. [262, 264, 267, 268, 281, 285, 286, 289] In general, there was not a consistent benefit of cognitive-focused activities across measures of attention, executive function, language, and memory compared with control conditions. In some cases, mixed effects were found within trials, with some domain-specific measures showing beneficial effects and other measures of the same domain finding no effect. Even within trials that reported both global cognitive function and domain-specific measures, results were inconsistent.

Physical function. Fifteen of the 28 trials reported physical function outcomes (ADL and/or IADL outcomes) with only 3 finding small but statistically significant improvements in measures of ADLs or IADLs among people with MCI or dementia at 5 to 12 months followup.[263, 280, 285] The remaining trials showed very little change over time for both intervention and control participants or small and relatively equal decline in measures of physical function over time.

Quality of life. Only 3 of the 12 studies that reported QOL outcomes reported small but statistically significant differences between cognitive-focused interventions and controls.[274, 276, 279] Only one of these studies also found significant benefit of cognitive training on global cognitive function; the other two trials found no other benefits of the interventions.

Neuropsychiatric symptoms. Changes in mental health and neuropsychiatric symptoms, including symptoms of depression and anxiety and behavioral problems, were reported by half of the studies (k=14). Again, there was no consistent pattern of effect across trials. Many showed relatively equal declines in self- or informant-based measures of depression or behavioral symptoms in both intervention and control group participants. Though the scales range considerably across these measures (e.g., 0–15 on the Geriatric Depression Scale, 0–38 for the CSDD; 0–144 for the Neuropsychiatric Inventory), most between-group differences did not exceed a 1-point difference in favor of either group.

Harms. One trial[278] reported no harms of a cognitive training and sham physical exercises over the course of the 6-month intervention. No other trial reported on harms that occurred during the study.

Exercise Interventions

Study and Population Characteristics

We included 21 trials (n=2,831), 6 of them good quality, that studied the effectiveness of an exercise intervention to improve cognitive function, physical function, and/or neuropsychiatric and depressive symptoms among adults with MCI or dementia. Fourteen of the 21 trials were newly identified as part of this update. Similar to the evidence on cognitive-focused interventions, the number of included participants in the exercise trials was quite small (median n randomized = 95; range 25–494) and the duration of the studies were short (14 of the 21 trials were 6 months or less in duration).

Just less than half of the studies targeted patients with MCI (mean MMSE score ranged from 24.5–27.4) and the other half targeted patients with dementia (mean MMSE score ranged from 18–26.4), one of which limited inclusion to patients with VaD.[291] Three trials included patients with MCI or dementia with one only enrolling older adults with serious mobility limitations.[295, 301, 308] Few studies reported what proportion of included participants was currently taking a cognitive medication. The mean age of patients ranged from 67 to 84 years. Both men and women were included in all trials, with most reporting an equal distribution of men and women. One trial[290] that had among the most intense exercise interventions (including strength and endurance activities) had a majority male sample (61%), whereas two trials[299, 308] of dancing interventions had a mostly female samples (78% and 82%). Only 4 of the 21 trials took place in the United States; the remaining 17 were in Europe (k=8), Asia (k=6), Australia (k=2), and Canada (k=1).

Intervention Characteristics

The included exercise interventions were highly variable across the trials. Most involved supervised group-based exercise sessions focused on aerobic activities, strength and resistance

training, and/or balance training that took place in a community setting and were led by an exercise specialist. Four trials included individualized, supervised exercise sessions in the home or community setting[290, 296, 301, 305] whereas three trials encouraged self- or caregiver-guided exercises at home.[292, 298, 303] Four trials evaluated the effectiveness of a group-based ballroom dancing intervention[299, 304] or dance-based intervention[306, 308] and two trials evaluated the impact of a Tai Chi program.[293, 309] Only a few studies mentioned specific cognitive training activities as part of the exercise intervention, including dual-task training (e.g., walking while counting backwards) and ballroom dance activities that involve physical, mental, creative, and social components. Interventions were relatively intense, with activities taking place 2-3 days per week for 30 minutes to 2 hours per session. Only six interventions, including the four dancing interventions, lasted more than 6 months.[290, 297, 299, 304, 306, 308]

In about half of the trials the comparison group consisted of an attention control including general health education relevant for older adults or brief interventions that included supervised "sham" exercise sessions focused on stretching or toning (k=9). In the remaining studies, control participants continued to receive usual care from their medical or memory-specific healthcare provider or were offered the intervention at the end of the trial (i.e., waitlist control).

Results

Cognitive function. All 21 trials reported a measure of global cognitive function or domain-specific cognitive function. Of the 14 trials that reported a measure of global cognitive function, all but two trials[300, 305] had sufficient data to meta-analyze results related to differences in change in the ADAS-Cog and/or MMSE measures at 3 to 12 months followup. Overall, there was mixed evidence related to the association between exercise interventions and improvement in global cognitive function at 3 to 12 months followup among patients with MCI or dementia. Effect estimates generally favored intervention groups compared with control groups, but findings were inconsistent across trials with nine of the 14 individual trials (6 among patients with MCI[292, 295, 297, 299, 304, 309] and 3 among patients with dementia[298, 302, 306, 319, 321, 322]) reporting a statistically significant benefit of the intervention compared with usual care or no intervention control groups on at least one measure of global cognitive function. The pooled analysis of 10 trials reporting results for the MMSE using resulted in small, statistically significant association (MD in change, 1.17 [95% CI, 0.45 to 1.90]; k=10; n=1,168; I^2=81.3%%) (**Figure 15**) However, the average mean difference in change in ADAS-Cog-11 scores across six trials that were pooled using the REML model with the Knapp-Hartung correction for small samples indicated no association (MD, -1.05 [95% CI, -3.49 to 1.10]; k=6; n=1,071; I^2=77.4%) (**Figure 16).** Results related to global cognitive function did not appear to differ according to different study (good vs. fair quality), population (MCI vs. dementia patients), intervention (duration of intervention, inclusion of any group sessions, specific type of exercise [e.g., aerobic activities, resistance training, ballroom dancing, Tai Chi), or control group (no intervention vs. brief or sham activities) characteristics.

Physical function. Change in physical function was variably measured across exercise trials including measures of impairment in ADLs (e.g., bathing, dressing, toileting, eating) with or without measures of impairment in IADLs (e.g., meal preparation, laundry, grocery shopping, travel, finances). Across eleven of the 21 trials measuring physical function, small improvements

were seen in the exercise groups within most trials whereas control groups reported worsening function over 3 to 12 months; five of the 11 trials reported these effects to be statistically significantly different between groups. A pattern was seen, though not definitive, where exercise interventions that included individually tailored instruction or self-guided instruction found effects on measures of ADLs or IADLs whereas those that employed supervised, group-based exercise sessions found no effect. This difference was not statistically tested, however, given the few studies reporting these measures and could be due to other confounding factors.

Quality of life. Only three studies that evaluated an exercise intervention reported a measure of QOL. In all three studies, self-reported or proxy-reported measures of QOL were nearly identical between groups after the intervention and inconsistent patterns of effects across different measures of QOL.

Neuropsychiatric symptoms. Ten trials reported the effects on symptoms of depression or other behavioral and neuropsychiatric symptoms; again, there was a pattern of effect favoring the exercise groups compared with the control groups but differences between groups were small and of unclear clinical magnitude.

Harms. Eight of the 21 trials (n=1,425) reported on harms of an exercise intervention.[290, 292, 301, 302, 304-306, 310] The most commonly reported AE in the intervention groups was musculoskeletal problems, including delayed onset muscle soreness, back pain, or specific joint pain. In terms of SAEs, in one trial[302] one case of atrial fibrillation experienced during one of the exercise sessions was deemed to possibly be related to the exercise intervention. In another trial of aerobic exercise,[301] one case of back pain related to spinal stenosis was judged to be exacerbated by exercise (either as part of the intervention or the battery of study measures that included a cardiorespiratory treadmill test). One other trial found eight AEs related to the intervention with four deemed as serious (one hospital admission for exercise induced angina, two injurious falls, and one case of substantially worsening hip pain).[306] Two trials[290, 302] reported no difference in the proportion of participants experiencing a fracture between intervention versus control groups. Other AEs reported during or following the exercise interventions were deemed by study researchers to not be related to the intervention.

Multicomponent and Other Interventions

Study and Population Characteristics

Sixteen trials (n=2,302), 12 of which are new to this update, included a multicomponent patient-level intervention or an intervention that was fundamentally different from the cognitive-focused and exercise interventions and therefore, are reported separately here (these latter interventions were categorized as “other”). Most were small trials (median n randomized=115; range 24–453) and 10 of the 16 studies took place for 6 months or less, whereas the other 6 ran for 7 to 24 months.

Intervention Characteristics

Each of these 16 trials evaluated different interventions. We categorized seven interventions as a multicomponent intervention. In these interventions, the primary aim was to investigate whether

these multicomponent interventions could slow the cognitive and functional decline of people with cognitive impairment and they typically consisted of a combination of group-based cognitive training and exercise with or without other components such as social activities or psychotherapy/cognitive behavioral therapy. The remaining nine trials, all conducted among patients with early-stage dementia, tested other unique patient-centered interventions. Interventions included diagnosis support and in-home counseling focused on patient well-being,[316] in-home counseling related to goal setting and action planning,[318] group-based psychotherapy and psychoeducation[315] or cognitive behavioral therapy[289] and a group-based self-management program.[314] Two trials focused on a multidisciplinary assessment and treatment plan coordination;[311, 313] one was specifically for patients with moderate-to-severe dementia who had recently transferred to a dementia-specific residential care facility (mean MMSE=14.8) One trial[317] aimed to slow functional decline among patients with mild dementia (not VaD) through pharmacologic and nonpharmacological vascular care (using ASA, vitamin B6, folate, statins, and, if indicated, therapies targeting blood pressure, glucose, smoking, and diet/activity). And, the last trial was a four-arm trial comparing the effects of exercise, dietary counseling, and exercise plus dietary counseling with an attention control focused on general cardiovascular health topics.[307] Comparison groups of these latter nine trials included usual care provided by general practitioners[313, 314, 317] or residential care staff,[311] a minimal intervention consisting of weekly home visits not focused on well-being, and a waitlist.[289, 315]

Results

Cognitive function. There was no clear effect for maintaining or improving global cognitive function in intervention groups compared with control groups. Only three individual trials[319, 321, 322] targeting mostly patients with MCI found statistically significantly different differences in global cognitive function at 6 to 9 months followup. The remaining trials showed generally null effects for both domain-specific and global measures of cognitive function, with effect sizes often favoring the control groups (many of which were quite intense in content and delivery). Pooling eight trials that included a multicomponent or "other" intervention that reported changes in MMSE score found an average mean difference between groups of 0.26 in favor of the intervention group, although the confidence interval reflected no difference between groups (95% CI, -0.54 to 1.00; k=8; n=1,238; I^2=30.3%).

Physical function. Changes in physical function were reported in only five trials with only one – a multicomponent group-based intervention with social, cognitive, and physical components over 6 months – finding a statistically significant benefit of the intervention. [322] The trial of multicomponent exercise and cognitive training,[278] cognitive behavioral therapy,[289] a multidisciplinary assessment and treatment plan,[313] and the trial of comprehensive vascular care[317] did not find that the interventions slowed the progression of decline in ADLs or IADLs at 3 to 24 months followup compared with sham activities or usual care.

Quality of life. The four trials focused on improving patients' well-being and QOL[289, 314-316] showed no clear benefit of the interventions on measures of QOL in comparison with control groups; only one trial reported greater improvement in the WHO Wellbeing Index (WHO-5) in intervention versus control participants at 6 months. But this same study found no difference in the EQ-5D measure of health-related QOL.[316] Likewise, one trial testing the effect of a

diagnostic assessment and comprehensive treatment plan found a small effect on caregiver-reported patient QOL at 6 months using the EQ-VAS, but not on other measures of QOL.[313]

Neuropsychiatric symptoms. There was no clear benefit of these multicomponent interventions or interventions aimed at well-being on any measure of symptoms of depression or anxiety or caregiver-ratings of neuropsychiatric symptoms.

Other outcomes. One study conducted a survival analysis of mortality and found a 63 percent lower risk of death in the multidisciplinary assessment intervention group compared with the usual care control group, although the difference was not statistically significant (95% CI, 0.22 to 1.15; p=0.08).[311]

Harms. Five trials[278, 310, 315, 319, 322] found no differences in the rate of harms between conditions; the remaining 11 trials did not report on harms.

Caregiver and Caregiver-Patient Dyad Interventions

We included 88 trials (n=14,880) that targeted the caregiver or caregiver-patient dyad with the primary aim of improving caregiver outcomes. Over one-third (33/88) of these trials were identified as part of this update and the remaining two-thirds (55/88) were included in the previous review. Most of the trials (k=58; n=9,139) evaluated interventions with some type of psychoeducational component for caregivers.[325-381] 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). Seventeen trials (n=3,039) provided case or care management directed at caregiver-patient dyad with or without psychoeducation for the caregiver.[382-398] The remaining 13 caregiver-focused intervention trials (n=2,702) evaluated other interventions such as physical activity counseling, social support interventions, and multicomponent dyadic interventions.[399-411]

There was no one consistent outcome reported across caregiver or caregiver-patient dyad intervention trials. The most commonly reported outcomes of these interventions were self-reported caregiver depressive and other mental health symptoms (reported in 62 of 88 trials) and caregiver burden (reported in 52 of 88 trials). Both outcomes were reported using a variety of self-reported measures. The Center for Epidemiologic Studies Depression Scale (CES-D) was the most commonly used instrument to assess symptoms associated with depression. Response options range from 0 to 3 for each item and scores range from 0 to 60, with high scores indicating greater depressive symptoms. For caregiver burden, the most commonly used instrument was the 22-item Zarit Burden Instrument (Zarit-22). The Zarit-22 measures perceived social, physical, financial, and emotional burden of caregiving, as well as providing a total summary score with a range of 0–88, where higher scores indicate greater burden. Rates of institutionalization or time to nursing home placement was often a primary outcome of caregiver-patient dyad interventions but should be interpreted alongside the results of other important caregiver and patient outcomes. While delay of institutionalization may be one of the most clinically important outcomes to examine within this field, it is potentially inappropriate if it is accompanied by declines in well-being on the part of family caregivers. Other outcomes such as caregiver and patient QOL were inconsistently reported.

Study, population, and intervention characteristics for all caregiver interventions are presented in **Table 19** and **Table 20**. Summary results are provided in **Table 21** and detailed results are provided in **Appendix H**.

Psychoeducation Caregiver Interventions

Study and Population Characteristics

We included 58 trials, representing over 9,139 caregivers or caregiver-patient dyads, that evaluated a caregiver psychoeducational intervention. Twenty-four of these trials are new to this update. We rated most of the studies fair quality given unclear allocation procedures, few baseline imbalances, and relatively high attrition (20–40%). Study sample sizes ranged from 28 to 642 participants, with most randomizing over 100 caregivers or caregiver-patient dyads. Most followed participants for at least 1 year, with three studies including longer-term followup at 3 or 4 years[344, 354, 376] and one including followup at 12 years.[365]

Almost three-quarters (74%, 43/58) of the trials targeted the caregiver only with the remaining targeting the caregiver-patient dyad (21%, 12/58) or entire family (5%, 3/58). Most trials required that caregivers provide support to the patient for at least 4 hours a day to be eligible for the study and many limited inclusion to caregivers reporting burden related to caregiving (e.g., Zarit burden score >22) or high psychological distress (e.g., >4 on General Health Questionnaire). Two trials prespecified inclusion to spousal caregivers,[357, 365] and one trial focused specifically on adult caregiving children of dementia patients.[344] When reported, the remaining trials included various proportions of spousal, child, and other nonprofessional caregivers. Caregivers were mostly female in all trials (range of female caregivers, 57–100%). The mean age of caregivers ranged from 41 to 75 years. Socioeconomic indicators such as education, income, and employment status were reported inconsistently and variably measured. Among those that reported educational level of caregivers, in most studies more than half of caregivers had at least a high school education with mean years of education ranging from 11 to 16 years. Race/ethnicity of caregivers was sparsely reported. Among the few trials that did report the race of participants, most caregivers and patients were white except for three trials[339, 342, 377] that were limited to Asian caregivers (2 trials in Hong Kong and 1 in the United States). Across all psychoeducation intervention trials, most took place in the U.S. (k=28) or western Europe (k=22). Four trials took place in East Asia (Hong Kong or Taiwan) and four took place in Canada.

In all but three trials, caregivers cared for patients with dementia, mostly characterized as Alzheimer's-type dementia. Two trials included caregivers of patients with either MCI or dementia,[343, 353] and one remaining trial[369] targeted caregivers of "frail community-dwelling older adults characterized as cognitively impaired" with an MMSE less than 23. The average MMSE scores across trials was consistent with patients having moderate, as opposed to mild, dementia (average MMSE score was 16.2 across studies that reported it). The mean age of patients ranged from 68 to 83 years.

Intervention Characteristics

The psychoeducation intervention trials encompassed a wide range of approaches. The most

common format was for interventionists to meet individually with caregivers, dyads, or families, most commonly in participants' homes (k=20). A number of the interventions, however, took place in group settings (k=18) or were provided remotely through telephone counseling, computer-based programs or applications, videos, or a combination of these methods (k=13). Across all psychoeducation interventions, in addition to providing information about dementia and community resources, most interventions also included training in problem solving, communication techniques, and stress management. A variety of additional components were used, including peer or social support (e.g., group support meetings or online forums to interact with peers, to express their concerns, discuss solutions to daily problems, and share their feelings and experiences), supportive counseling (counseling focused on the caregiver's emotional or psychological issues), home safety assessments or information, occupational therapy, and environmental modifications. The interventionists were also highly variable, reflecting the specific components within each intervention and included general educators or counselors, psychologists, nurses, occupational therapists, social workers, and hired and trained research staff. Only two interventions included contact with a geriatrician.[335, 374] The majority of interventions were relatively short (median=4 months) but ranged from 1 month to 2 years, and participants generally meet every 1 to 3 weeks over the course of the interventions.

Most trials included a usual care control group (k=22) or attention controls where caregivers received similar or slightly less contact with an interventionist who provided general dementia education with or without nondirective social support (k=21). The remaining trials included no intervention or waitlist control groups. Usual care was rarely fully described. When it was, most mentioned usual memory or primary care for patients with referrals to outside organization or community resources for caregiver support.

Results

Although there were substantial clinical differences among the interventions evaluated, overall there was a consistent finding of a benefit on caregiver burden and depression outcomes in people caring for patients with mostly moderate dementia. Effect sizes were mostly small, however, and few of the individual trials reported statistically significant differences between groups.

Caregiver burden. The standardized pooled effect for trials reporting sufficient data to be included in the meta-analysis (k=27; n=2,776) showed a small but statistically significant effect (SMD, -0.24 [95% CI, -0.36 to -0.13]; I^2=50.2%) (**Figure 17**). We could not include nine of the trials that reported burden in the meta-analysis because of missing data (e.g., variance) or reporting of an incompatible outcome. [328, 332, 338, 344, 363-365, 370, 381] In these studies, the effect sizes were similarly small, with few finding statistically significant group differences.[344, 365]

The clinical importance of these changes in self-reported caregiver burden scores is unclear. Most studies reported group differences between 0.5 and 5 points on a scale of 0–88 on the Zarit-22. Baseline Zarit-22 scores ranged widely across studies from an average of around 23 to 56 points, and only one study reported average changes of greater than 2.5 points over 6 months followup in the intervention group. To aid in interpretation, we pooled the nine trials that reported change in the Zarit-22 and found an average 2.5-point difference favoring the

intervention group versus control group (MD, -2.47 [95% CI, -3.91 to -1.03]; k=9; n=1,089; I^2=0%) (forest plot not shown). This is equivalent to a change from being bothered "always" to "sometimes" or "almost never" on one of the 22 items. Across all measure of burden, the confidence intervals of the study-level between-group differences were frequently quite wide, suggesting the possibility that some caregivers showed substantial improvement or benefit in their perceived burden and others did not benefit. Unfortunately, we could not identify what subgroups of caregivers may have benefitted based on study-level data.

Caregiver mental health. Forty-three of the 58 psychoeducation trials reported a measure of caregiver depressive symptoms, using a variety of self-report instruments. Like findings for caregiver burden, the effect sizes for depression outcomes across all trials were relatively small and imprecise. Our meta-analysis included the pooled effect for 37 comparisons (n=4,555) and found a small but statistically significant effect favoring the intervention on depression measures at 3 to 12 months followup (SMD, -0.26 [95% CI, -0.39 to -0.13]; I^2=76.9%) (**Figure 18**). In most cases, caregivers in the intervention groups reported experiencing fewer depressive symptoms over time, whereas caregivers in the control groups reported slightly more symptoms or little change over time. The CES-D, a 20-item instrument (scale of 0-60 with lower scores equaling fewer depressive symptoms), was the most commonly used instrument. Pooling the 20 trials that reported CES-D-measured depressive symptoms resulted in a between-group mean difference of 2.67 points favoring the intervention group (MD, -2.67 [95% CI, -3.85 to -1.48]; k=20; n=2,603; I^2=65.1%) with most trials reporting an approximate 1- to 5-point difference (forest plot not shown). Similar to changes in caregiver burden, the clinical importance of these small changes in depression scores is unclear. A 3-point difference could mean that a person moved from endorsing a single symptom 5 to 7 days to rarely or never in the previous week, or from 3 to 4 days to 1 to 2 days for three symptoms in the previous week.

We could not include 12 trials that reported a measure of depressive symptoms in the meta-analysis due to missing data.[325, 326, 333, 338, 344, 348, 360, 369, 370, 381, 386, 412] In five of these trials, study authors reported statistically significant benefit of the interventions on depressive symptoms.[326, 348, 360, 386, 412] Five trials did not report depressive symptoms but reported measures of other mental health symptoms such as anxiety, perceived stress, and psychological morbidity.[331, 350, 361, 362, 374] These trials, as well as others that reported such measures, found similar patterns of effects with intervention participants reporting slight improvements in mental health symptoms while control group participants reported similar scores over time. Few trials, however, reported statistically significant differences between groups over time.

For both caregiver burden and caregiver depressive symptoms, we visually explored the summary tables and forest plots and ran exploratory meta-regressions to determine if any design, population, or intervention feature explained the variability in effect sizes. These variables included study quality (good vs. fair), new versus previously included trials, U.S.- versus non-U.S.-based trials, mean baseline MMSE of patients being cared for, type of control group (minimal or brief intervention vs. usual care, waitlist, or no intervention), target audience (caregiver and patient or whole family vs. caregiver only), intervention duration, setting of intervention [home vs. not in home], primary intervention format (individual- vs. group-, family-based, or telehealth interventions), and key intervention strategies (training and support vs. training only). For caregiver depression, there was evidence of a difference in effect based on the

type of control group. A statistically significant favorable effect was found when comparing psychoeducation interventions with no treatment or usual care control groups (SMD, -0.44 [95% CI, -0.65 to -0.24]; k=20; n=2,347; I^2=81.3%), whereas no effect was found when comparing psychoeducation interventions versus attention controls consisting of brief or minimal interventions (SMD, -0.09 [95% CI, -0.25 to 0.06); k=15; n=1,873; I^2=60.6%) (p-value for difference = 0.036). This same effect was not seen for the outcome of caregiver burden (p=0.815). None of the other variables robustly predicted larger effect sizes for measures of caregiver burden or caregiver depression.

Caregiver quality of life. Only 16 of the 58 trials reported effects of the interventions on caregivers' assessments of their QOL. Patterns of change over time were inconsistent between trials with some trials showing improved mean scores in both intervention and control participants, some showing decreased scores in both groups, and some reporting improvement in intervention participants with declines in control group participants. Seven of the 16 trials reported some statistically significant differences in favor of the intervention groups, but almost all only reported this for one of many measures of QOL within the study or only at shorter versus longer followup.[339, 349, 355, 357, 362, 376, 377]

Decision making. One fair-quality trial (n=111) reported the effects of a psychoeducational intervention on caregivers' reports of planning or decision-making related to caring for their relative with dementia.[336] The aim of this study was to test the efficacy of the "Learning to Become a Family Caregiver" program intended for caregivers following the diagnostic disclosure of Alzheimer's disease in a relative. The intervention, delivered through seven 90-minute individual sessions over 2 months, was designed to foster a successful transition to the caregiving role by acquiring certain skills to manage stress, plan, and care for a relative. Caregivers randomized to the control arm received usual care provided by local memory care clinics which consisted of putting caregivers in contact with a range of local available services. The relatives with dementia did not take part in the intervention; patients in both groups continued to attend the memory clinics as needed. Three months following the intervention (5 months postbaseline assessment), caregivers in both groups reported statistically significantly better planning for the future care needs of the relative with no difference between groups. Using a six-item Likert-type scale with a range of 6–30 where higher scores equaled greater planning, scores among intervention participants increased from a mean (standard deviation) of 15 (5.84) to 19.67 (5.78). whereas scores for control participants increased from a mean of 15.04 (6.90) to 18.36 (6.84) and no group-by-time effect was found.[336]

Patient institutionalization. In terms of patient outcomes, 10 of the 54 trials reported rates of institutionalization or time to nursing home placement as primary or secondary outcomes.[326, 344, 354, 355, 365, 373-376, 381] Half of these trials took place in the United States, and most provided followup for 1 year or longer (including 4 trials with 3 or more years followup). Only two trials, both evaluating a version of the New York University Caregiver Intervention (NYUCI), reported statistically significantly favorable effects of the interventions on delaying patient institutionalization.[344, 365] In the first trial among spousal caregivers, after 9.5 years of followup, patients whose spouses received the intervention experienced a 28.3 percent reduction in the rate of nursing home placement versus usual care controls (HR=0.717 [95% CI, 0.537 to 0.958], p=0.0247).[342] In the second trial, adapted for adult child caregivers in Minnesota (NYUCI-AC),

after 2 years, two-thirds (66%) of adult child caregivers in the control condition admitted their parent to a residential care setting (assisted living, family care home, or nursing home) compared with 37 percent in the treatment condition. Logistic regression and Cox proportional hazards models found that NYUCI-AC participants were significantly less likely ($p<.05$) to admit their parents to a residential care setting and delayed their parents' time to admission significantly longer (228.36 days longer on average) than those in the control group.[344] In both trials, favorable benefits were also seen for outcomes of caregiver stress, burden, depression, and QOL measures. Other trials reported data on numbers of participants being institutionalized when describing participant attrition; those data are not presented here.

Other patient outcomes. Additional patient outcomes were inconsistently reported across the trials and included changes in patients' global and cognitive function, ADLs and IADLs, mental and behavioral health symptoms, and QOL. Few trials reported statistically significant favorable effects on such outcomes.

Harms. Only three trials (n=326) monitored adverse events during the trial period. Neither found any harms of the intervention.[349, 357]

Care/Case Management

Study and Population Characteristics

We categorized 18 interventions in 17 trials as care or case management interventions (n=3,039). We broadly labeled these interventions as care or case management if the intervention included professional assistance to help arrange, implement, or facilitate services to meet a patient's and family's needs. In all cases, care management was intended for both the caregiver and the patient with dementia (or the patient's entire family). One trial[398] extended existing care coordination for patients by also providing care coordination support for caregivers through a personalized caregiver support plan. Six of these 17 trials were new to this update, two of which took place in the United States.[392, 395]

Four were cluster RCTs, randomizing at the level of the primary care clinician[383, 396] or practice.[394, 397] Six trials took place in the United States, six in Europe (Finland, Germany, or Netherlands), one in Australia, three in Hong Kong, and one in Canada. Most recruited participants from primary care,[383, 389, 390, 392, 394, 396, 397] with the remaining recruiting from memory clinics or other outpatient clinics,[386, 391, 393] health plan membership,[382] local Alzheimer's organization,[384] or other social services or self-referred methods.[385, 387, 388, 395, 398] Sample sizes ranged from 72 to 516 caregiver-patient dyads. Collectively, trials within this category of intervention provided the longest followup, with all but one[392] following participants for a year or longer. Eight of the 18 trials provided results at 1.5 or 2 years followup.

All care management interventions were intended for patients with dementia. Two trials also included a small proportion of participants with MCI,[393, 395] and one trial enrolled health plan members whose medical records indicated they had a dementia diagnosis or a symptom code indicating memory loss.[382] Baseline mean MMSE scores of patients ranged from mild dementia (22.8) to moderate dementia (13.8). Few (7 trials) reported the proportion of patients being treated for dementia with medication; in those that did, 27 to 78 percent of patients were taking

an AChEI. One trial required patients to be on a stable dose of an AChEI to be eligible for the study.[392]

Two trials included only or mainly spousal caregivers;[388, 392] the others included a fairly even distribution of spouse, child, and other relational caregivers. The mean age of caregivers ranged from 44 to 75 years old while the mean age of patients ranged from 68 to 84. Most caregivers in each trial were female. The gender distribution of patients within trials was more evenly distributed and ranged from 38 to 68 percent females, where reported. Extremely limited data about the race/ethnicity, education, or other socioeconomic variables were provided for patients or caregivers.

Intervention Characteristics

While each intervention was unique, the interventions we categorized as care or case management generally all provided assessment, advice and information, individualized treatment planning, caregiver psychoeducation and skills training, ongoing monitoring, and either referral or care coordination with outside social and health care services (such as occupational and physical therapy, respite care, personal care assistance, social, and social work). Two interventions in the United States were partnerships between an Alzheimer's Association chapter and a managed care plan[382] or primary care physicians[389] to provide care consultation and individualized treatment plans to families. One trial in the Netherlands compared the effectiveness of care coordination and postdiagnosis treatment provided by a memory clinic with the same service provided only by a general practitioner.[393] Finally, one trial in Germany provided training for primary care physicians on non-medication-based and medical treatment options for dementia and information and counseling for caregivers; in one intervention arm, the physician suggested that the caregiver attend support groups and receive counseling for up to 2 years, and in the other arm, the physician made the same suggestion but for up to 1 year.[394] These interventions were longer than any other category of intervention in general, providing support and care management to caregivers and patients for a year or longer (range 3 months–2 years, median=1 year).

All but two interventions were primarily provided through individual in-person interaction with or without other delivery methods such as group sessions or support groups, telephone contact, or mailed print materials. In the remaining two interventions, information, counseling, and coordination were provided solely by telephone.[382, 392] The interventionists varied, but most often included a nurse or other health provider serving as a "case manager" or "care coordinator." Other providers included primary care clinicians, geriatricians, occupational therapists, neurologists, psychiatrists, social workers, and other research staff. Many interventions took a team approach, with different providers providing different components of the intervention. Interaction mostly took place in participants' homes but planning and counseling also took place in a medical setting (i.e., primary care clinic, dementia-specific clinic).

In all trials, the control group consisted of usual care provided by primary care or a memory-specific clinic or organization (k=12) or another minimal intervention (k=5). Usual care varied, based on the study's setting, including country. In most cases, patients continued usual medical care with their primary provider and were given information on other local social and health

services. The two trials that partnered with Alzheimer's Association chapters acknowledged that the control group participants had access to their normal managed or primary care and were able to contact the association independently and use any of its services other than care consultation. The five trials that included minimal attention control groups provided enhanced support for caregivers (e.g., individual counseling sessions) in addition to usual care for patients.

Results

The primary outcome or outcomes of the 17 trials of care and case management interventions differed across trials and included time to institutionalization or nursing home admissions,[386-389, 394, 395] caregiver outcomes such as burden, strain, caregiving competence and QOL,[382, 384-386, 391-393, 396-398] mental and neuropsychiatric symptoms of the patient,[383, 392, 396] and patient QOL.[393, 397]

Patient institutionalization. Ten of the 17 trials reported rates of patient institutionalization or time to institutionalization. There was a pattern of benefit among patients in intervention versus control groups, with fewer people in the intervention groups placed in nursing homes than those in usual care or a delayed time to institutionalization among intervention versus control participants. Those with dementia who were placed in nursing homes ranged from 5.5 to 32.1 percent among adults in the intervention groups and from 1.5 to 33 percent in the control groups at 1 to 2 years followup. Only three trials reported statistically significant differences related to institutionalization, but all three measures also included other health care utilization or survival measures such as death.[384, 385, 395] In the two disease management trials in Hong Kong, both found significantly less frequent and shorter rates of placements and stays in residential homes or hospital units, including temporary hospitalizations, over the previous 6 months.[384, 385] In the 18-month MIND care coordination trial, intervention participants were less likely to permanently leave their home or die compared with controls (30.9% vs. 45.6%; p=0.012) and remained in their homes significantly longer (mean 496 days vs. 445 days; p=0.02). The hazard of leaving the home was decreased by 37 percent after adjusting for whether the caregiver lived in the home (HR, 0.63 [95% CI, 0.42 to 0.94]; p=0.022).[395]

This MIND care coordination trial was the only trial to include a measure of unmet care needs related to dementia.[395] Using the Johns Hopkins Dementia Care Needs Assessment, evaluators assessed 19 common care needs for participants (71 items) and caregivers (15 items) each as being "fully met" or "unmet." A total percent of unmet needs was calculated ([# of unmet needs/# of needs assessed] *100) as well as the proportion of unmet items in six specific areas: evaluation and treatment of memory symptoms; neuropsychiatric symptom management; home and personal safety; general, specialist and allied health care; daily and meaningful activities; and legal issues/advanced care planning. After 18 months, there was no statistically significant group difference in reduction of total percent of unmet needs; however, the intervention participants had a significantly greater reduction in the proportion of unmet needs in the two domains of safety and legal/advance care planning domains relative to control participants.[395]

Caregiver burden. A benefit of care and case management on caregiver burden relative to usual care or other minimal interventions was evident. The effects were relatively larger than those seen for other types of caregiver interventions. Of the 12 trials reporting a measure of caregiver burden, 5 found a statistically significant benefit of caregiver interventions after 6 to 18 months.

The combined standardized effect was -0.54 (95% CI, -0.85 to -0.22; k=8; n=1,215; I^2=82.9%) (**Figure 17**) among the eight trials that could be pooled, translating to a between-group difference of approximately 3.5 to 4 points on the Zarit-22. Statistical heterogeneity was substantial, consistent with the clinical heterogeneity among the trials and interventions themselves.

Caregiver mental health. Fewer trials (k=7) reported caregiver depression outcomes. While effects trended toward a benefit of care management interventions, the effects were small, and a meta-analysis of available data indicated no association (MD, -0.13 [95% CI, -0.29 to 0.02]; k=4; n=668; I^2=0%) (**Figure 18**).

Caregiver quality of Life. Caregiver QOL was again variably measured, and while self-reported QOL tended to improve in intervention participants and decrease in control participants, few trials reported consistent favorable effects across measures or time.

Other patient outcomes. In terms of patient outcomes, there were mixed findings related to behavioral and neuropsychiatric symptoms, measures of depressive symptoms, and QOL, with some trials finding very small benefits of the intervention on such outcomes and others finding no effects. Besides the one trial that reported a measure unmet care needs related to care coordination, no other trial reported on how care or case management interventions impacted clinician, patient, or family decision-making.

Harms. None of the trials of care or case management interventions reported on adverse events related to the trial.

Other Caregiver and Caregiver-Patient Dyad Interventions

Study, Population, and Intervention Characteristics

We included 13 additional trials (n=2,702) that evaluated a caregiver or caregiver-patient dyad intervention that were unique in their intervention and were categorized as "other" interventions. Only three of these trials were new to this update. Interventions were: physical activity counseling for the caregiver; a multicomponent dyadic intervention; social support only; assessment and treatment planning or multidisciplinary assessment only; or another intervention.

Three fair-quality trials (n=293) focused on increasing physical activity of caregivers with a primary aim of reducing caregiver burden and improving caregivers' QOL.[400, 402, 403] All recruited caregivers of people with dementia. One trial in the United States limited inclusion to female caregivers[403] and another, also in the United States, comprised only spousal caregivers (all of whom ended up being female).[400] The remaining trial in Japan recruited caregivers living with the person with dementia.[402] The majority of women in both U.S. trials were white (>85%); race/ethnicity of caregivers in the Japanese trial was not reported. All three interventions included very little in-person contact with caregivers; rather, counseling and physical activity prescriptions were provided entirely via video and telephone,[400] telephone only,[403] or a one-time prescription for caregivers to participate in moderate-intensity physical activity and pedometer and journal for recording activity.[402] Two additional trials (1 good-quality trial and 1 new fair-quality trial) (n=264) evaluated multicomponent dyadic interventions that included exercise

training, psychoeducation, and skills training to both patients and caregivers in their homes for 3 to 6 months.[408, 410] Each had slightly different aims. In the new trial in the Netherlands, both patients with mild dementia (MMSE=21.0) and the caregivers with whom they lived with simultaneously received exercise training, psychoeducation, communication skills training, and pleasant skills training in an attempt to improve patients' mood, behavior, and physical function as well as caregivers' mood and perceived burden.[408] In the older, good-quality trial, patients with moderate dementia (MMSE=16.7) received exercise training and their caregivers received psychoeducation with an aim of reducing functional dependence and delaying institutionalization of the patient with dementia.[410]

Three additional fair-quality trials (n=486) tested the effects of a caregiver social support intervention on caregivers' QOL and well-being.[399, 407, 411] Two trials took place in the United States, while the other took place in the United Kingdom. All caregivers were caring for people with dementia, although the severity of dementia was not reported. Most caregivers were female in all three trials (range 64–100%). In two trials, peer volunteers were matched with caregivers and provided informational and emotional support through weekly home visits over the course of 2[407] or 6 months.[399] In the other, telephone-based support groups were offered to caregivers through 26 weekly calls over 6 months.[411]

Three fair-quality trials (n=1,341) focused on providing comprehensive medical and cognitive assessments, including an assessment of caregivers' impressions and well-being, and providing a standardized treatment plan.[401, 405, 406] One each took place in the United States, Australia, and France. In all cases, people with moderate dementia (MMSE range 16.6 to 19.7) and their caregivers took part in the intervention. The intensity of the interventions varied: in the US-based trials, participants took part in 8 sessions over 4 month, in the trial in Australia, patients and caregivers attended a hospital memory clinic on two occasions over the course of a year, whereas in the trial in France, dyads met with a multidisciplinary team twice a year for 2 years.

One additional good-quality trial in the Netherlands (n=301) tested the impact of a provider training program to train professionals in the assessment of and strategies for reducing caregiver burden.[409] And, the final new, good-quality trial evaluated the effects of a Transcendental Meditation® program on the stress and QOL of 17 dementia caregivers in Australia.[404]

Results

None of these trials showed a consistent benefit on patient or caregiver outcomes compared with control conditions. The pooled effects of the few trials reporting caregiver burden (**Figure 17**) or caregiver depressive symptoms (**Figure 18**) found inconsistent and imprecise results. Only one trial (n=160) reported adverse events experienced by the caregivers, with none occurring in either goup over the course of the 2-month intervention.[401]

Chapter 4. Discussion

Summary of Evidence

We did not identify any direct evidence on the benefits and harms of screening for cognitive impairment, although there is one in-process trial that may help address this issue. As such, our review answers two primary 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 mild to moderate dementia or MCI? We identified over 260 studies that addressed these questions, more than a quarter of which were identified as part of this update. Despite the accumulation of new data, we believe that the conclusions are concordant with the findings of the previous review.[104, 105]

Table 22 presents our summary of findings for all KQs as well as our assessment of the strength of evidence for each body of evidence.

Screening

Our review identified a very large body of well-conducted test-accuracy studies that evaluated brief screening instruments in unselected, community-dwelling older adults. In general, these instruments have adequate sensitivity (mostly ≥75%) and specificity (mostly ≥80%) to detect dementia, although estimates vary and the optimal diagnostic thresholds or cutoffs for many of these instruments are unclear. Across all instruments, sensitivity was generally higher in the detection of dementia than in the detection of cognitive impairment (inclusive of MCI alone or MCI and dementia diagnoses), although the confidence intervals often overlapped and the cutoffs were not always adjusted to identify a lower level of impairment. Because many instruments focus preferentially on memory dysfunction (as opposed to other domains of cognitive function) it is thought that some instruments may perform better (or more consistently) for different types of dementia. For instance, memory loss is the hallmark of AD dementia but is not necessarily impaired at an early stage with other types of dementia. Unfortunately, most studies did not specify what types of dementia were identified, although most cases are presumed to be Alzheimer's.

Even though this is a large body of evidence, only a handful of instruments have been evaluated in more than one study and few are very brief instruments that may be more applicable to primary care. The MMSE is the most thoroughly studied instrument, but it has a relatively long administration time (~7–10 minutes) and is not available for use without cost. Our bivariate pooled analysis for the MMSE at a cutoff of ≤23 or ≤24 (≤23 is the recommended cutoff) resulted in 89 percent sensitivity (95% CI, 0.85 to 0.92; I^2=58.7%) and 90 percent specificity (95% CI, 0.86 to 0.93; I^2=97.4%) (k=14, n=11,972) to identify dementia. Among the other instruments examined in at least two studies with adequate test performance to detect dementia among primary care-relevant populations, are: *very brief instruments* such as the Clock Drawing Test, the Memory Impairment Screen (MIS), which includes the Memory Impairment Screen Telephone and Mental State Questionnaire, the Mini-Cog, verbal fluency tests, the AD8, and the Functional Activities Questionnaire; *brief instruments* such as the Abbreviated Mental Test ,

Montreal Cognitive Assessment, 7-Minute Screen, and Saint Louis University Mental Status Examination; and the *longer, self-administered* Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) short and long forms. Four of these instruments (the Mini-Cog, MIS, AD8, and short IQCODE) and the General Practitioner Assessment of Cognitive (GPCOG) are endorsed by the Alzheimer's Association, Gerontological Society of America, or National Institute on Aging for use in primary care. In all cases, administration of these structured screening instruments is advised if signs or symptoms of cognitive impairment are present upon review of a health risk assessment or through clinical observation or if concerns are raised by the patient or informant.[102, 103, 413]

Hypothesized Benefits and Harms of Screening

Hypothesized benefits of screening for, or early detection of, cognitive impairment include the ability to: 1) optimize current medical management (e.g., search for potentially treatable or reversible disorders such as medication interactions, depression, and thyroid disease), factor in patient comprehension of and compliance with treatment plans and other conditions, avoid medications with anticholinergic effects, and better manage related symptoms, such as depression and irritability; 2) enhance understanding of the disease, including its symptoms and course and thereby help caregivers and patients better adapt to and manage the diagnosis; 3) help ensure appropriate access to programs and services for patients and families; and 4) ensure risk reduction (e.g., consider strategies to prevent delirium, motor vehicle accidents, medication errors, and financial difficulties).[414] Perhaps the best rationale to routinely screen for cognitive impairment in older adults is that early diagnosis can positively influence decision-making that leads to improved patient outcomes and reduced future costs. This may include facilitating involvement of patient and caregivers in planning medical, educational, and psychosocial interventions to suit their needs; starting early so the patient can still participate in medical, legal, and financial decisions; and making proxy plans.[414] While these are all logical arguments, there is currently little or no empirical evidence, including qualitative evidence, to support them.[415]

Screening for cognitive impairment may also have direct or indirect harms as a result of diagnostic inaccuracy (false-positives and false-negatives) and because of the negative emotions and stigmatization that may arise once the patient is diagnosed.[416, 417] We found no trial evidence however, to substantiate or refute concerns about harms of screening. Recent systematic reviews regarding patients' attitudes and preferences about screening for dementia found mixed evidence. Some studies suggested that patients have no concerns and welcome having their memory evaluated, whereas others suggested that few people would agree to routine screening for memory problems for reasons such as stigma.[415, 418] Additional cross-sectional evidence in this review suggested that caregivers and the general public believe they will benefit from being screened for dementia, in part because there are effective treatments and financial benefits.[415, 419, 420] However, a few studies suggest that a high proportion (48 to 67%) of patients who screen positive for cognitive impairment refuse a diagnostic evaluation.[421, 422]

Some studies suggest that a dementia diagnosis can be difficult for patients, whereas others find no deleterious associations. One recent study found that patients experienced higher stress, greater depression, and lower QOL with awareness of their diagnosis of MCI or early-stage AD versus those who were unaware of their condition.[423] Similarly, another study found that older adults who knew they were ApoE4 carriers reported more symptoms of cognitive decline and

performed more poorly on measures of memory than adults who were ApoE4 carriers but had no information about their genetic risk.[424] Other studies, however, have found no association between a formal dementia diagnosis and poor psychological health outcomes.[425-429] Given the cross-sectional nature of the data, these studies have many limitations, and none provided a comprehensive look at the harms (or benefits) of routine screening.

Treatment

Our review was not a comprehensive synthesis 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 or MCI (i.e., those populations more representative of screen-detected older adults with cognitive impairment). We reviewed available pharmacologic interventions in the United States, including FDA-approved medications for use in AD such as AChEIs and memantine, potentially disease-modifying medications (i.e., antihypertension therapy, HMG Co-A reductase inhibitors, NSAIDs, and gonadal steroids), and vitamins and supplements. Nonpharmacologic interventions represented in this review included focused and complex interventions aimed at the patient (i.e., cognitive-focused interventions, exercise interventions, and multicomponent interventions) and focused and complex interventions aimed at the caregiver or caregiver-patient dyad, including psychoeducation and care management or care coordination interventions.

Overall, based on the large body of evidence, AChEIs (donepezil, galantamine, and rivastigmine) and memantine can improve global cognitive function in the short term. The improvements seen, however, are small and may not be clinically important. On average, differences between people taking these medications versus those receiving placebo favored the medications by only about 1 to 2.5 points on the ADAS-Cog and 0.50 to 1.25 points on the MMSE. The values commonly accepted as clinically important are an ADAS-Cog change of 4 points or more (on a scale of 0–70) or a MMSE change of 3 points of more (on a scale of 0–30).[106] Given the consistency in the effect estimates across trials and precision in these estimates over time, we are moderately confident that our pooled estimates and the results of the body of evidence lie close to true effects. While measures of global function were less commonly reported, they were still reported in most medication trials. AChEIs and memantine increased the likelihood of improving or maintaining patients' global function by 15 percent (for memantine) to 50 percent (for rivastigmine) in the short term (generally 6 months or less) as compared with placebo. There was limited evidence about the effects of these medications on measures of physical function and other important patient-reported outcomes, and the measures showed mixed results when they were reported. None of the trials of medications reported QOL outcome measures. Almost all available evidence is from trials in people with dementia, particularly those with Alzheimer's disease and those with moderate as opposed to mild forms of dementia. Evidence for these medications in people with MCI is much more limited. Trials of donepezil and memantine in patients with MCI showed no benefit on global cognitive function or in the rate of conversion from MCI to AD.

Side effects are common with all these medications and discontinuation due to adverse effects from AChEIs, but not memantine, was higher in treatment groups than in control groups. While

there did not appear to be an increase in serious adverse events in the medication trials of limited duration, some of the individual studies, including observational evidence, reported increased rates of bradycardia, and relatedly, of syncope, falls and need for pacemaker placement among those exposed versus unexposed to AChEIs. We did not abstract and analyze common adverse reactions, but the types and relative frequencies are well-described.[430] The most common side effects 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). 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).

We have limited confidence in the evidence regarding effects of other medications, vitamins, and supplements on important functional outcomes. Although some individual trials reported promising effects particularly for vitamin E supplementation, in general, there was no consistent benefit on cognitive or physical function among those with mild to moderate dementia or MCI within each class of therapy. Harms of these agents were not clearly higher in intervention groups than in control groups.

Most of the new evidence in this review is related to nonpharmacologic patient interventions, namely cognition-focused interventions and exercise interventions among those with mild to moderate dementia (not identified through screening). While there was a relatively large number of studies, most of the individual trials were small (<100 participants). There was no overall evidence that cognitive stimulation, training, or rehabilitation improved global or domain-specific measures of cognitive function at 3 to 12 months followup. Effect estimates generally favored the intervention groups over control groups, but the magnitude of effect was inconsistent in trials and represented very wide CIs (ranging from no effect to a large effect). While a pooled analysis of cognitive training, stimulation, and rehabilitation intervention trials found a small, statistically significant mean difference of about 1.5 points on the MMSE, there was substantial clinical and statistical heterogeneity. Furthermore, there was no overall pooled difference between groups when looking specifically at measures on the ADAS-Cog. There was also no evidence that the effect of the interventions was modified based on study, population, or intervention characteristics and no evidence of longer-term effects on cognitive function. Only about half of the trials evaluating cognition-focused interventions reported other important patient outcomes such as measures of ADLs and IADLs, neuropsychiatric symptoms, or QOL, with most finding very little change over time in both intervention and control participants or small and relatively equal decline in these measures over time. Though the scales range considerably, the majority of between-group differences did not exceed a 1-point difference in favor of either group on any of these measures. Similarly, trials of exercise interventions resulted in no marked improvement in measures of global or domain-specific cognitive function compared with no intervention or usual care. There was a favorable pattern, however, for the effect of exercise interventions on measures of physical function, with those taking part in exercise interventions experiencing small improvements of unclear clinical significance (e.g., by approximately 1 point), whereas control groups reported worsening function over 3 months to 1 year. This evidence is limited by possible selective reporting (only half of the exercise trials

reported this outcome) and considerable heterogeneity in the instruments used to measure these outcomes. Likewise, there was a pattern of effect favoring the exercise groups compared with the control groups for measures of global cognitive function and neuropsychiatric and behavioral symptoms, but differences between groups were small and of unclear clinical magnitude. There were no clear benefits of multicomponent or other patient-level nonpharmacologic interventions on any important patient-reported outcome. Even those trials that specifically targeted improvements in patients' well-being and QOL found no differences between groups on these measures. Regarding all types of patient-level interventions, potential harms were rarely reported. Given the considerable heterogeneity both in the clinical characteristics of these trials and the lack of consistency and precision in the effect sizes across trials, we have low confidence that the pooled effects and patterns of effects we report in this review reflect true average effects. The heterogeneity in each individual intervention arm and differences in the populations, settings, and trial quality made it difficult to disentangle what variables might be driving larger effects, even within subgroups of interventions.

The largest body of evidence in our review included trials evaluating interventions targeting caregivers of those with dementia or the caregiver-patient dyad. Almost all the included evidence pertained to patients (or their caregivers) with dementia; very few included any patients with MCI. Further, most trials represented patients with moderate as opposed to mild dementia and none of the interventions were linked with a standard screening program. In general, these individual trials were larger and longer in duration than the other nonpharmacologic studies (likely due to the younger age and relative health of caregivers compared with patients and therefore, a greater ability to minimize loss to followup). Among trials evaluating a psychoeducation intervention for caregivers, we found that these interventions can reduce caregiver burden and depression more so than no intervention, usual care, or other brief interventions, but the average effects for both outcomes were small. Interpretation of the pooled standardized effect sizes and their 95 percent CIs ranged from very small (about 0.1) to small (about 0.3), representing between-group differences of approximately 0.5 to 3.5 points on the Zarit-22 (88-point scale) or 1.5 to 4 points on the CES-D (60-point scale). In most cases, caregivers in the intervention groups reported experiencing fewer depressive symptoms or a reduced burden over time, whereas caregivers in the control groups reported slightly more symptoms or little change over time. Slightly larger effects on caregiver burden were seen among trials evaluating comprehensive care or case management interventions. The pooled effects of care management interventions versus usual care or other brief interventions on caregiver burden indicated small (0.2) to large (0.8) effects, translating to a between-group difference of approximately 3.5 to 4 points on the Zarit-22. While effects trended toward a benefit of care management interventions on caregiver depression, the effects were small, and pooling all available data indicated no association. Regarding both outcomes and trials, the 95 percent CIs of the study-level between-group differences were often wide, suggesting a range in benefit (or lack thereof) across participants. There was no evidence in our meta-regressions, however, that one type of intervention (psychoeducation vs. care or case management vs. other caregiver or caregiver-patient dyad interventions) was more effective than the others regarding measures of caregiver burden or caregiver depression. Likewise, there were no study, population, or intervention characteristics that consistently and robustly predicted larger effects on caregiver burden or depression outcomes.

Many of these interventions, particularly those employing care management programs, had explicit goals to maximize the ability of both patients and caregivers to keep patients at home or in assisted living settings and out of skilled nursing facilities. There was a pattern of benefit where fewer people in the intervention group were placed in nursing homes (or experienced delayed time to institutionalization) compared with those in usual care, but very few trials found these differences to be statistically significant. While delay of institutionalization may be one of the most clinically important outcomes to examine within this field, it is potentially inappropriate if it is accompanied by increased stress or negative mental and physical health on the part of family caregivers.[431, 432] Few studies, however, have examined this relationship. Other outcomes such as caregiver or patient QOL, patient mental health and neuropsychiatric symptoms, and patient functional ability were sparsely reported across the trials, with no consistent evidence of a benefit. Decision-making and preparation for meeting dementia-related needs were only reported by one trial each, with neither finding statistically significant benefit of the interventions versus control conditions on overall scores for these measures. Only two trials reported monitoring harms related to the caregiver interventions and no harms were evident.

Comparison With Other Existing Systematic Reviews

The findings of our review are consistent with the conclusions of other recent systematic reviews that have examined the test performance of instruments to detect dementia or MCI.[433, 434] Even with the expansion of scope in these other systematic reviews (e.g., inclusion of any clinical setting, case-control studies), these other reviews also concluded the MMSE is the most-studied instrument with test performance similar to what was seen in our review (pooled sensitivity and specificity of 0.71 and 0.74 to detect MCI and 0.81 and 0.89 to detect dementia). They additionally note that several instruments have comparable test performance as the MMSE, such as the Mini-Cog or MoCA.

Likewise, the findings of our review are generally concordant with those other recent systematic reviews that have synthesized the evidence on the benefits and harms of pharmacological and nonpharmacological interventions in people with MCI and mild-to-moderate dementia. Similar to our review, most of the identified recent reviews of trials testing the effectiveness of AChEIs and memantine found short-term small statistically significant improvements on global cognitive function and global function, as well as increased risk of adverse events compared with placebo groups.[435-440] Likewise, our findings on the benefits and harms of other medications, vitamins, and supplements are consistent overall with those of comparable reviews, with primarily null findings across all reported outcome types.[441-444]

Furthermore, recent reviews of trials evaluating patient-level cognitive-focused and physical activity interventions accord with our findings in that there was little-to-no benefit of the interventions on global and domain-specific cognitive function.[323, 324, 445] Similar to our review, one review of physical activity interventions found a minor improvement in physical function.[445] On the contrary, evidence from recent reviews of studies targeting caregivers of people with dementia was less consistent with our findings.[446-449] That is, three of the four identified reviews found no benefit for caregiver burden, with inconsistent findings for other outcomes (e.g., depression, quality of life, anxiety) associated with counseling, case management, and

mindfulness-based stress reduction interventions. These discordant findings are primarily due to key differences in scope resulting in lesser evidence bases in each of the respective reviews.

Implementation of Screening

Our review included an examination of brief screening instruments that could be 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. Most of the included instruments are available in the public domain, although the MMSE (which remains the best-studied instrument) is a notable exception. 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 cognitive impairment, including issues regarding 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.

Routine Screening vs. Case Finding

There is disagreement about the best approach to detect cognitive impairment. Many believe the best approach is to routinely administer a brief cognitive test to *all* older adults or older adults above a specified age, then provide a diagnostic evaluation or referral for those whose scores are consistent with possible dementia. Also recommended is a stepwise approach of administering a brief cognitive test only to people at high risk for or who have suspected cognitive impairment based on clinician observation, self- (or informant-) reported concerns, or review of a health risk assessment or single item indicating subjective cognitive complaints or concerns related to one's everyday function. This approach can be viewed as a two-step screening process *or* a case-finding approach: screening with a question on cognitive complaints and an assessment of ADLs/IADLs, followed by administration of a brief instrument designed to assess cognitive impairment. We found no evidence to support or refute this proposed method. We did, however, find one study that used electronic medical record data to identify patients at increased likelihood of having undiagnosed dementia based on their history of stroke and emergency department visits and found a higher likelihood of dementia diagnoses among that group versus controls.[450] Our review focused on screening among older adults without known cognitive impairment and therefore did not address the use of brief cognitive instruments in people with observed deficits (i.e., case-finding). We did, however, include studies that enrolled patients with subjective memory complaints, given the high prevalence of memory complaints in general among older adults. No pattern was seen in the test performance or prevalence of dementia for these studies compared with those that did not have a subjective memory complaint requirement. Further research comparing which criteria (e.g., age, comorbid conditions, functional status, self-reported memory complaint) should lead primary care clinicians to conduct cognitive screening, and perhaps how often screening should be conducted, is needed.

Age at Which to Start (and Stop) Screening

Age is the biggest risk factor for cognitive impairment. Therefore, if screening is advisable, 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 age 75 and rises to approximately 10 percent among 75 to 84-year-olds and nearly 30 percent among those 85 years and older.[4, 23]

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. 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 60 percent if the prevalence of underlying dementia approximates 30 percent (**Table 23**). The general prevalence is much lower in populations younger than age 85 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.

Screening Interval

Likewise, 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 grows exponentially with age, and the estimated doubling time of AD incidence in North America is 6 years.[27, 451] Incidence rates from one U.S.-based longitudinal cohort study demonstrated 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.[452] 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 cutoff for an 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 cutoffs, may vary depending on the stakeholder's resources and preferences.

Limitations of Our Approach

Our review has several limitations given our primary aim and target audience—the USPSTF. It was relatively narrow in scope and was not meant to be a comprehensive review of all cognitive screening instruments nor all dementia treatments. We focused on the best-quality evidence for the diagnostic accuracy of cognitive screening instruments in community-dwelling older adults relevant to primary care in the United States. Therefore, we excluded case-control studies, instruments with lengthy administration times, and studies among institutionalized adults or among those selected based on cognitive impairment or clinically suspected cognitive impairment. Additionally, we did not address other important aspects of screening test performance, including the psychometric properties of instruments (besides sensitivity and specificity), the comparative performance of screening instruments, and the ability to improve diagnostic performance by combining screening instruments.

Likewise, our review focused on best-quality evidence for interventions applicable to community-dwelling older adults with screen-detected cognitive impairment. We included only evidence among older adults (or their caregivers) with mild to moderate dementia or MCI and excluded studies among institutionalized older adults and those with severe dementia, trials of experimental therapy, and interventions aimed primarily at symptom management. Despite our best efforts, there may have been some inconsistency in operationalizing these inclusion criteria and in categorizing the interventions due to reporting in individual trials. We also did not address the comparative effectiveness of different types of interventions. Given the heterogeneity in the included evidence, even within subgroups of interventions, we were unable to explain important population or intervention characteristics that predicted larger effects or the minimum components of effective interventions.

Limitations of the Studies and Future Research Needs

Despite such a large body of research on the test accuracy of screening for cognitive impairment, as well as treatment and management of people with dementia and MCI, there are several important limitations and research gaps in the evidence base. First is the lack of evidence around decision-making outcomes. Experts in the field argue that early diagnosis is important because it influences clinical and patient decision-making. While this is a reasonable argument, there is currently little to no empirical evidence to support it. Researchers should conduct screening trials or observational studies to demonstrate changes in decision-making (at a minimum) and patient or caregiver outcomes (as an ideal). Studies examining how (and whether) earlier identification of cognitive impairment or earlier management of patients with dementia and their caregivers influence clinician decision-making (e.g., medical management of comorbid conditions) and patient and family decision-making (e.g., advanced planning) are critical to improving management of this rapidly growing health care problem.

Second, 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. Others have argued that the harms of screening and mislabeling people 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 whether, harmful tradeoffs exist.

Third, while there are many well-designed diagnostic accuracy studies, there has been very little reproducibility in testing instruments, at consistent cutoffs and for specific conditions, in primary care populations. Well-conducted diagnostic accuracy studies for the most promising instruments or those currently endorsed in national guidance need to be reproduced in relevant populations. These diagnostic accuracy studies should report adequate baseline population characteristics, including age and education (characteristics 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). Furthermore, studies should be explicit in describing which types of dementia were identified and have large enough samples to report the test accuracy of the instrument in detecting different forms of dementia.

Fourth, 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 focused on early (even preclinical) detection of disease.[453] 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 be manifested.[454]

Fifth, a major limitation in the treatment literature is the short followup duration (generally 6 months or less for pharmacologic trials and 1 year or less for nonpharmacologic trials). Dementia is a chronic condition that worsens over time; while one year of observation provides time to monitor changes in most outcomes, it does not provide a long enough observation period for more distal outcomes such as nursing home placement or mortality. Indeed, most of the included evidence did not include reports on rates of institutionalization or mortality, nor was it powered to detect differences in such outcomes. We acknowledge, however, that trials in older adult populations with longer duration and followup run the risk of heightened attrition due to institutionalization and mortality in addition to more general tendencies of attrition seen in longer-term studies.

Sixth, there are numerous challenges surrounding measurement within the treatment literature. In general, trials offer little consistency in the specific outcomes reported. Even within specific outcomes, the wide variation in the measures make cross-study comparisons difficult. A strikingly high number of trials do not fully describe the instruments, including the scale range or direction of benefit, used to measure key outcomes. This makes it nearly impossible to determine the magnitude of change reported in individual studies or to combine seemingly "like" outcomes in pooled analyses. In some cases, in order to be able to combine the most studies possible, we calculated standardized mean differences rather than mean differences according to the original scale of the instruments. These standardized effect sizes are generally harder to interpret and give no indication of the meaningfulness of any differences seen. Where we could, we provided an estimate of what the effect would be based on a standardized effect size to add in interpretation. Development of a set of agreed-upon patient and caregiver measures like those being populated

in the National Institutes of Health Patient-Reported Outcome Measurement Information System would advance this area of research considerably.[455]

Seventh, the average treatment effects revealed by this body of evidence 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) for patients with less pronounced cognitive impairment. For example, the ADAS-Cog and MMSE may have ceiling effects and therefore be unable to show benefit in people with MCI or even mild dementia. Other important outcomes, such as global function, physical function, QOL, and institutionalization, were inconsistently reported (except for the CIBIC+, 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 followup is limited. 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.

Eighth, the overwhelming majority of evidence is in people with AD, and additional research is needed on the effectiveness of various interventions in other types of dementia, including VaD, FTD, and DLB.

Finally, while our report did not evaluate the effectiveness of experimental therapies targeted to alter the disease process, disease-modifying therapies (e.g., those targeting amyloid-related mechanisms or tau-related mechanisms) to slow cognitive decline are an extremely active area of research.[453] If these therapies are found to truly alter the disease process, there may be reason to change the benefit-to-risk ratio, which could have implications for routine screening for cognitive impairment.

Conclusions

Several brief screening instruments can adequately detect cognitive impairment, especially in populations with a higher prevalence of underlying dementia. There is no empiric evidence, however, that screening for cognitive impairment or early diagnosis of cognitive impairment improves patient, caregiver, family, or clinician decision-making or other important outcomes. Harms of screening for cognitive impairment are not well studied. There is a robust evidence base studying pharmacologic and nonpharmacologic interventions aimed at improving patient function and caregiver well-being. In general, there is support that AChEIs and memantine and interventions that support caregivers, including those that help coordinate care for patients and caregivers, can result in small improvements in the short term. Unfortunately, the average effects of these benefits are quite small and likely not of clinical significance. Additionally, most of the evidence pointing to positive effects is applicable to people with moderate—as opposed to mild—dementia. Therefore, the applicability of the treatment evidence to people with screen-

detected cognitive impairment is unclear. Any benefits are further limited by the commonly experienced side effects of medications and the limited availability of complex caregiver interventions. Cognitive stimulation and training, exercise interventions, and other medications and supplements showed some favorable effects on patients' cognitive and physical function, but trial evidence lacked consistency and the estimates of benefit were imprecise. There is less evidence related to screening for and treating MCI. The test performance of the few instruments evaluated to detect MCI was lower than the sensitivity and specificity to detect dementia, despite more liberal cutoffs, and there is little evidence for any pharmacologic or nonpharmacologic interventions to preserve or improve patient functioning in people with MCI.

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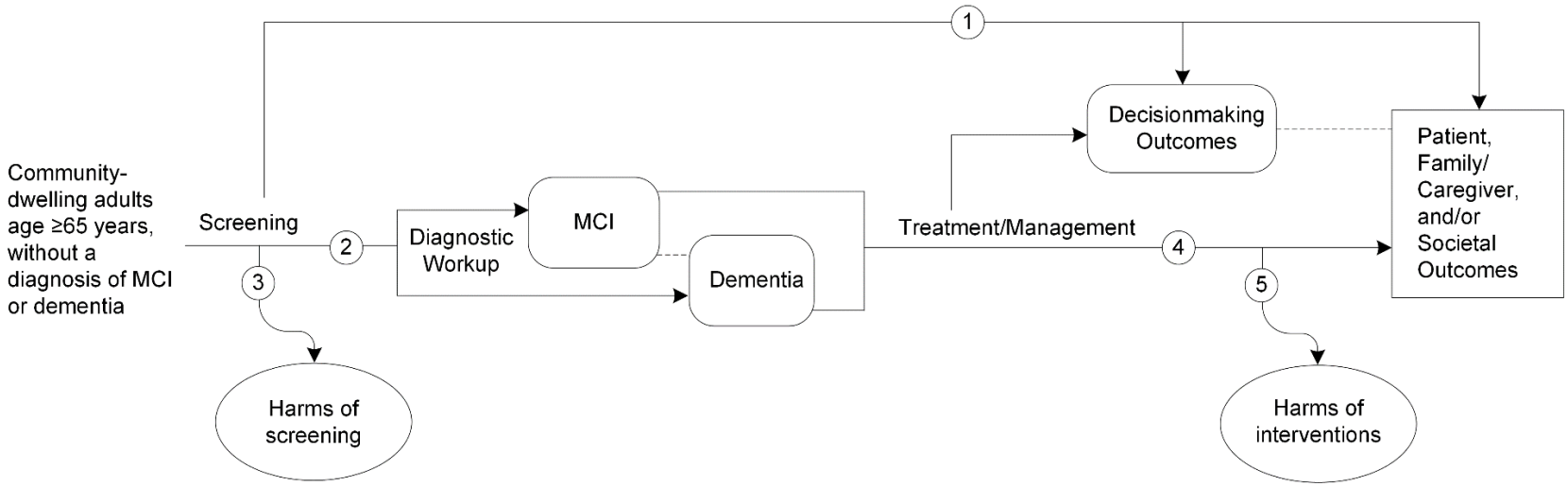
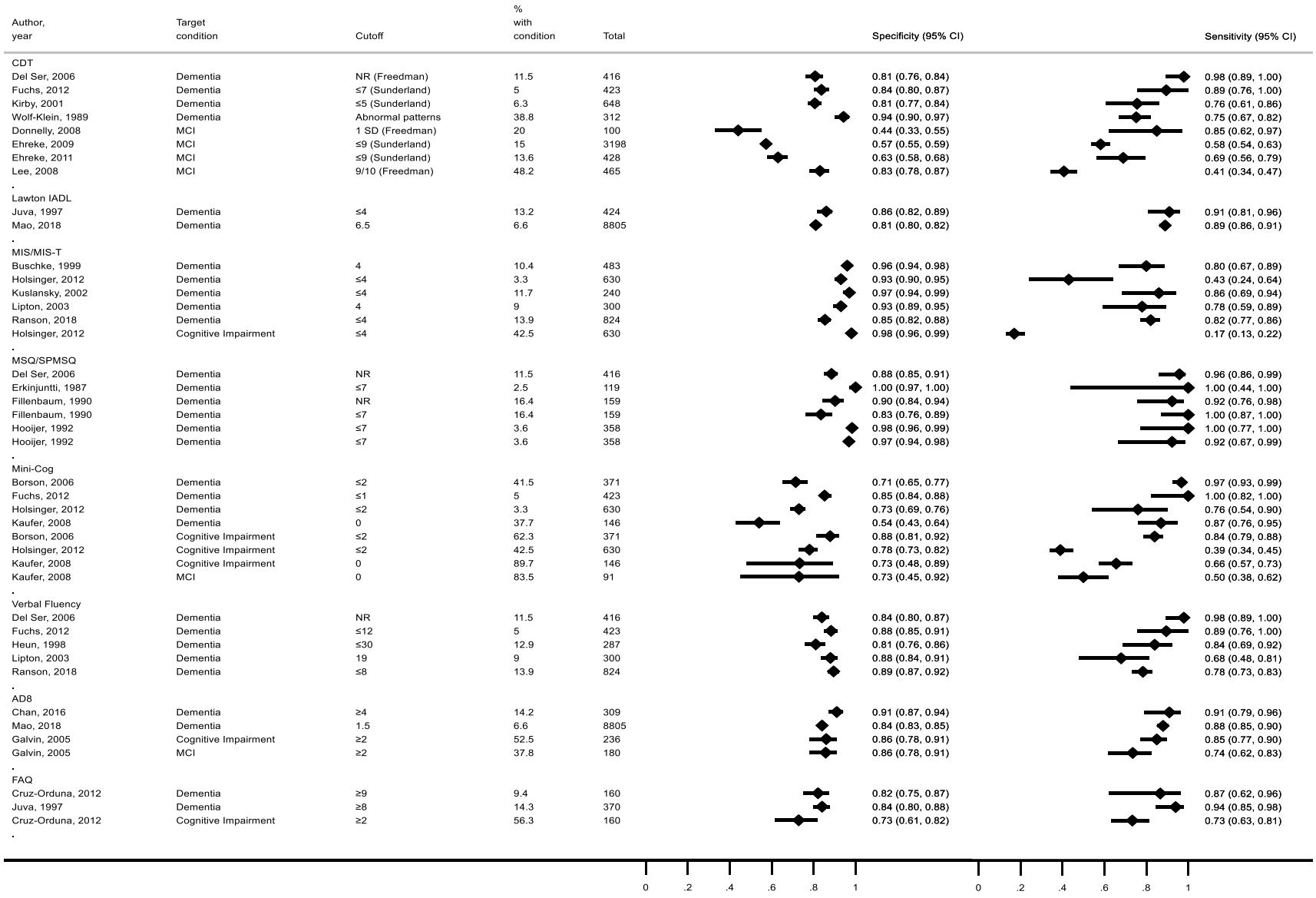
Figure 1. Analytic Framework



Abbreviation: MCI=mild cognitive impairment.

Figure 2. Test Accuracy of Very Brief Screening Tests Reported in More Than One Study (KQ 2)



* MIS-T
† MSQ
‡ Informant target

Figure 2. Test Accuracy of Very Brief Screening Tests Reported in More Than One Study (KQ 2)

Abbreviations: AD8 = 8-item informant interview; CDT = Clock Drawing Test; CI = confidence interval; FAQ = Functional Activities Questionnaire; KQ = key question; MCI = mild cognitive impairment; MIS/MIS-T = Memory Impairment Screen/Memory Impairment Screen by Telephone; MSQ/SPMSQ = Mental Health Status Questionnaire/Short Portable Mental Status Questionnaire; NR = not reported

Figure 3. Test Accuracy of Very Brief Screening Tests Reported in One Study (KQ 2)

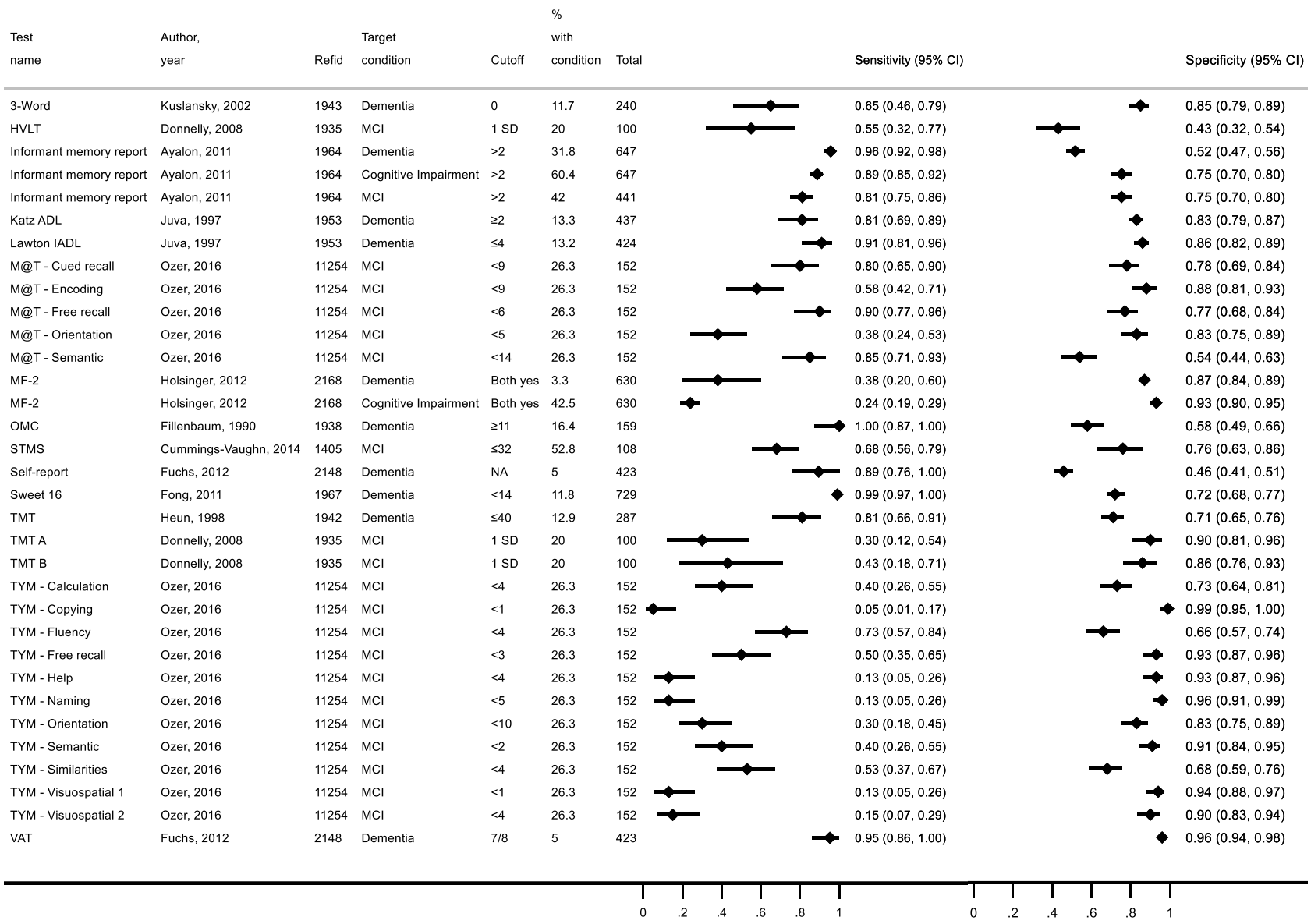
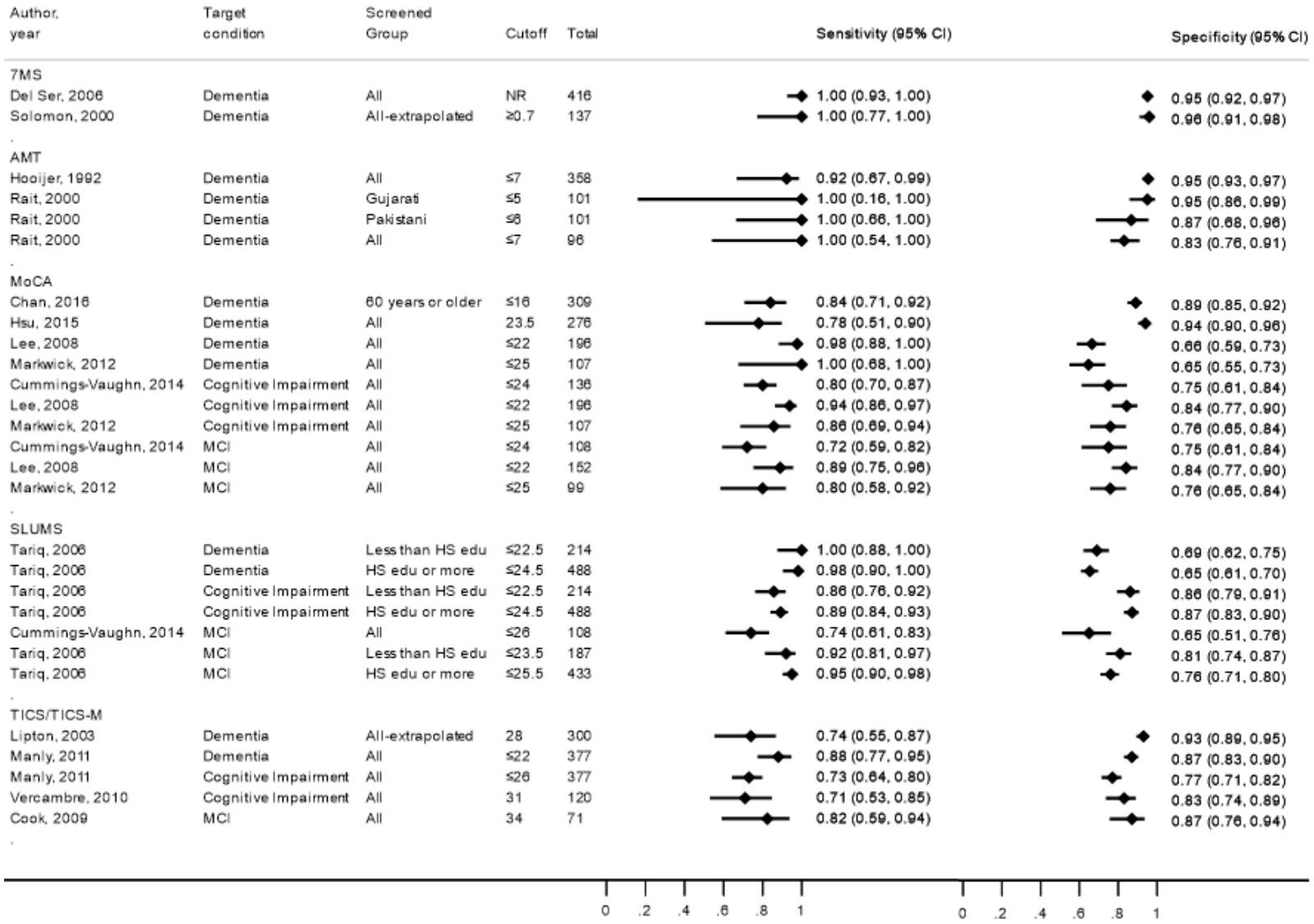


Figure 3. Test Accuracy of Very Brief Screening Tests Reported in One Study (KQ 2)

Abbreviations: 3-Word = 3-Word Memory Test; ADL = activities of daily living; CI = confidence interval; HVLT = Hopkins Verbal Learning Test; IADL = instrumental activities of daily living; KQ = key question; M@T = Memory Alteration Test; MCI = mild cognitive impairment; MCI = mild cognitive impairment; MF-2 = 2-item functional memory screen; NA = not applicable; OMC = Orientation Memory Concentration; SD = standard deviation; STMS = Short Test of Mental Status; TMT = Trail Making Test; TYM = Test Your Memory; VAT = Visual Association Test

Figure 4. Test Accuracy of Brief Screening Tests Reported in More Than One Study (KQ 2)



Abbreviations: 7MS = 7-Minute Screen; AMT = Abbreviated Mental Test; CI = confidence interval; HS edu = high school education; KQ = key question; MCI = mild cognitive impairment; NR = not reported; SLUMS = Saint Louis University Mental Status Examination; TICS/TICS-M = Telephone Instrument for Cognitive Status/Telephone Interview for Cognitive Status modified

Figure 5. Test Accuracy of Brief Screening Tests Reported in One Study (KQ 2)

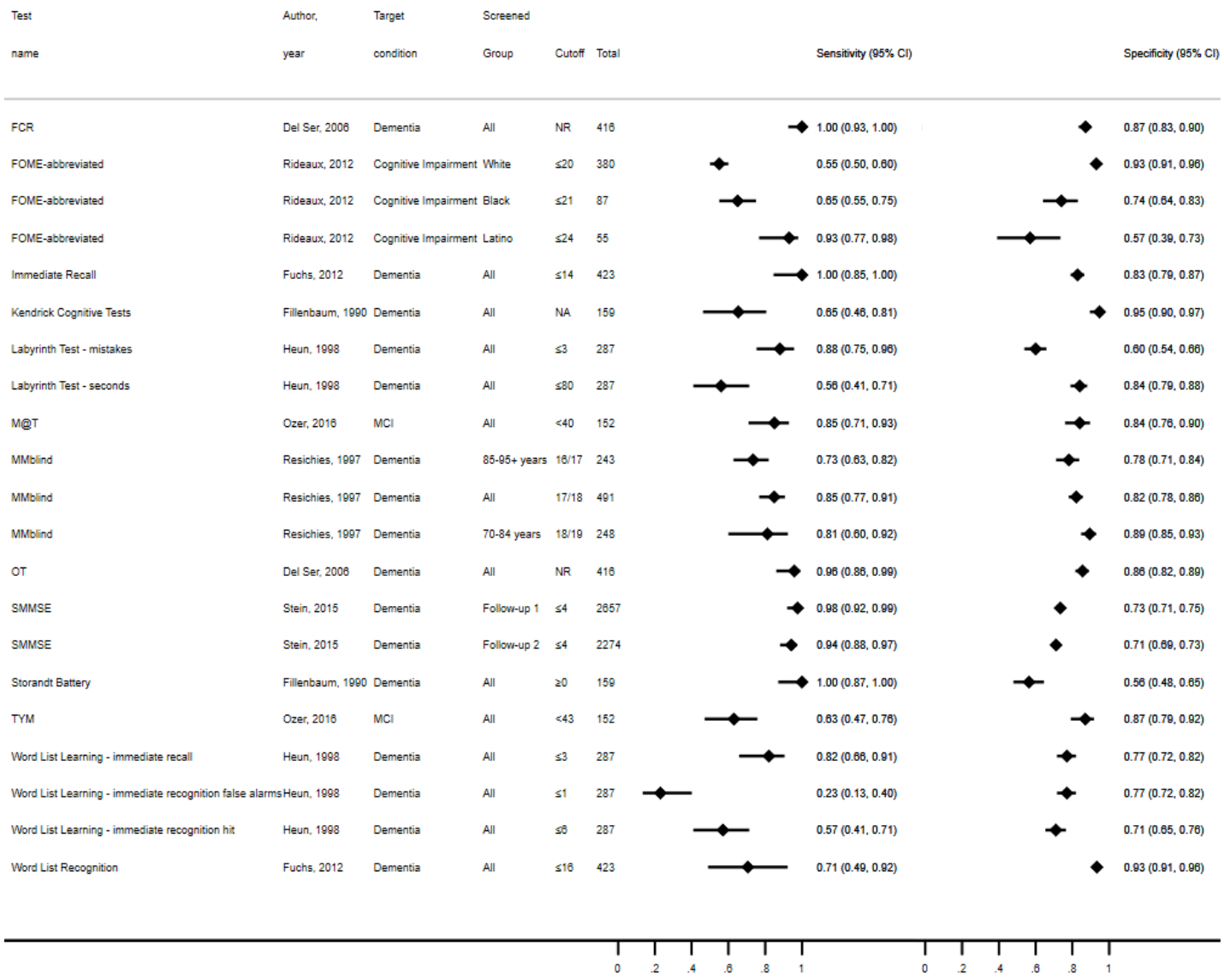
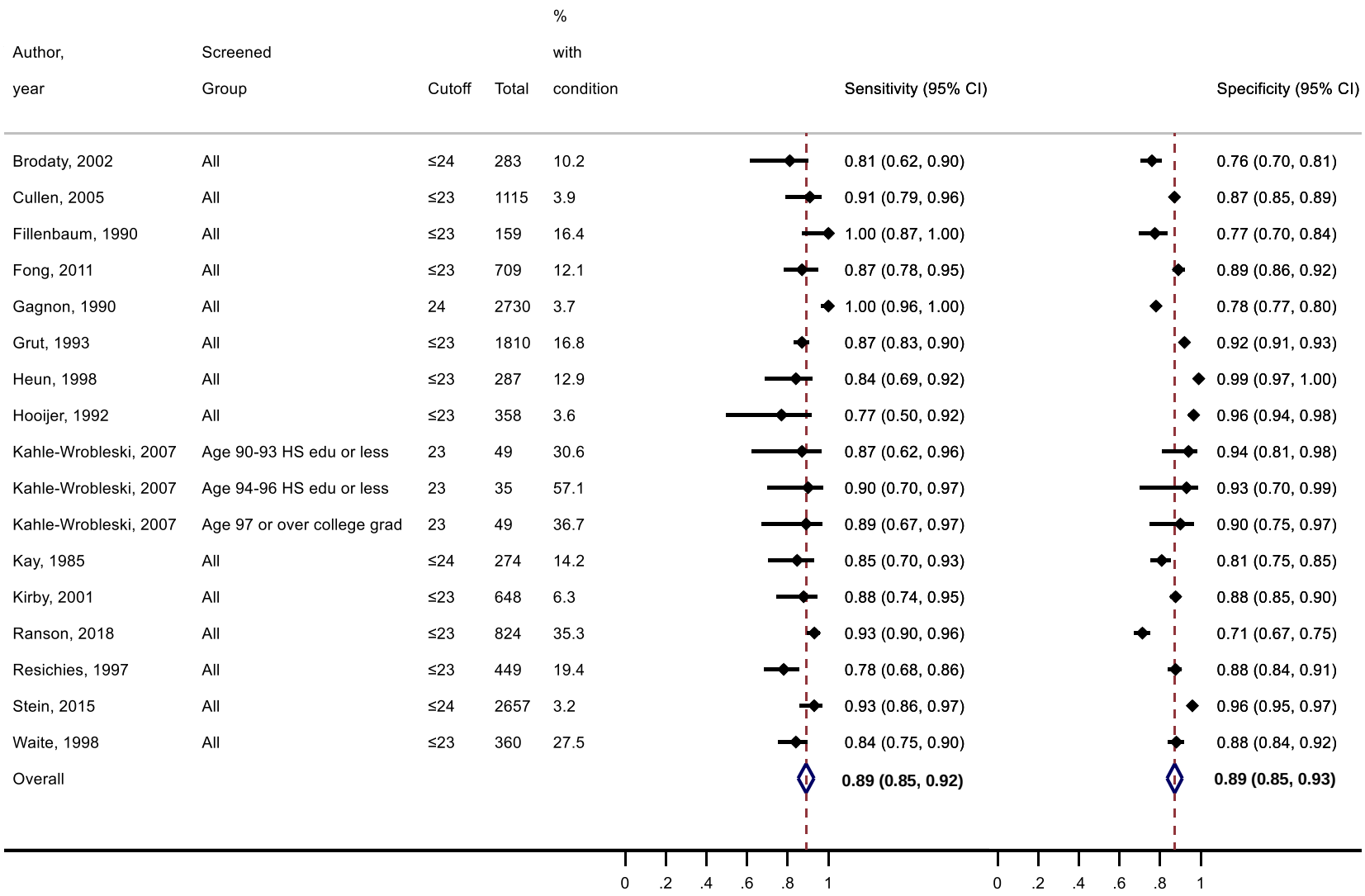


Figure 5. Test Accuracy of Brief Screening Tests Reported in One Study (KQ 2)

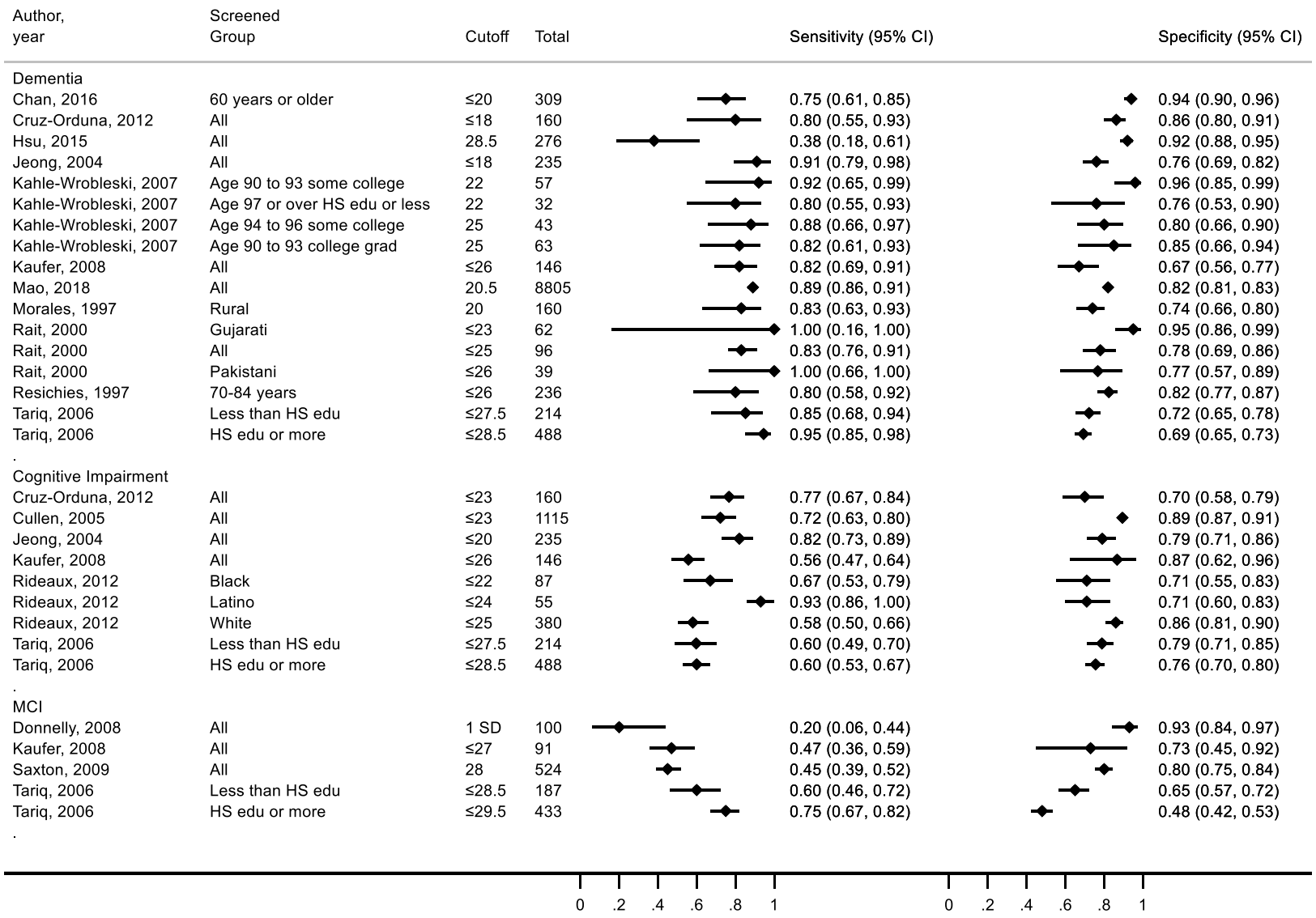
Abbreviations: CI = confidence interval; FCR = Free and Cued Recall; FOME = Fuld Object Memory Evaluation; MMblind = MMSE version for persons with visual impairment; KQ = key question; MCI = mild cognitive impairment; NR = not reported; SLUMS = Saint Louis University Mental Status Examination; TICS/TICS-M = Telephone Instrument for Cognitive Status/Telephone Interview for Cognitive Status modified

Figure 6. Bivariate Pooled Analysis of Test Accuracy of the MMSE to Detect Dementia at a Cut-Off of ≥23 or ≥24 (KQ)



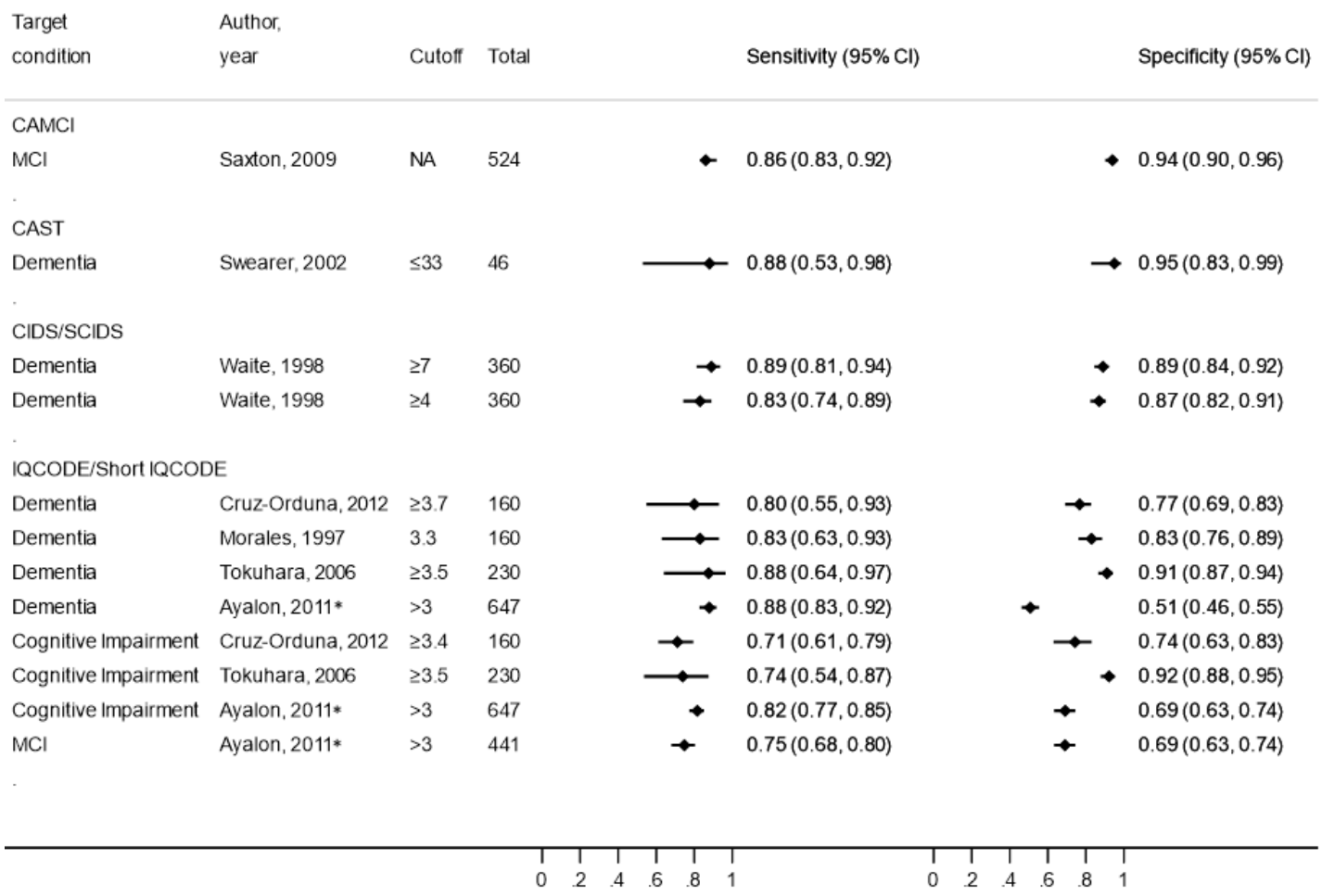
Abbreviations: CI = confidence interval; HS edu = high school education; KQ = key question; MMSE = Mini-Mental State Examination

Figure 7. Test Accuracy of the MMSE at Other Cut-Offs (KQ 2)



Abbreviations: CI = confidence interval; HS edu = high school education; KQ = key question; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination

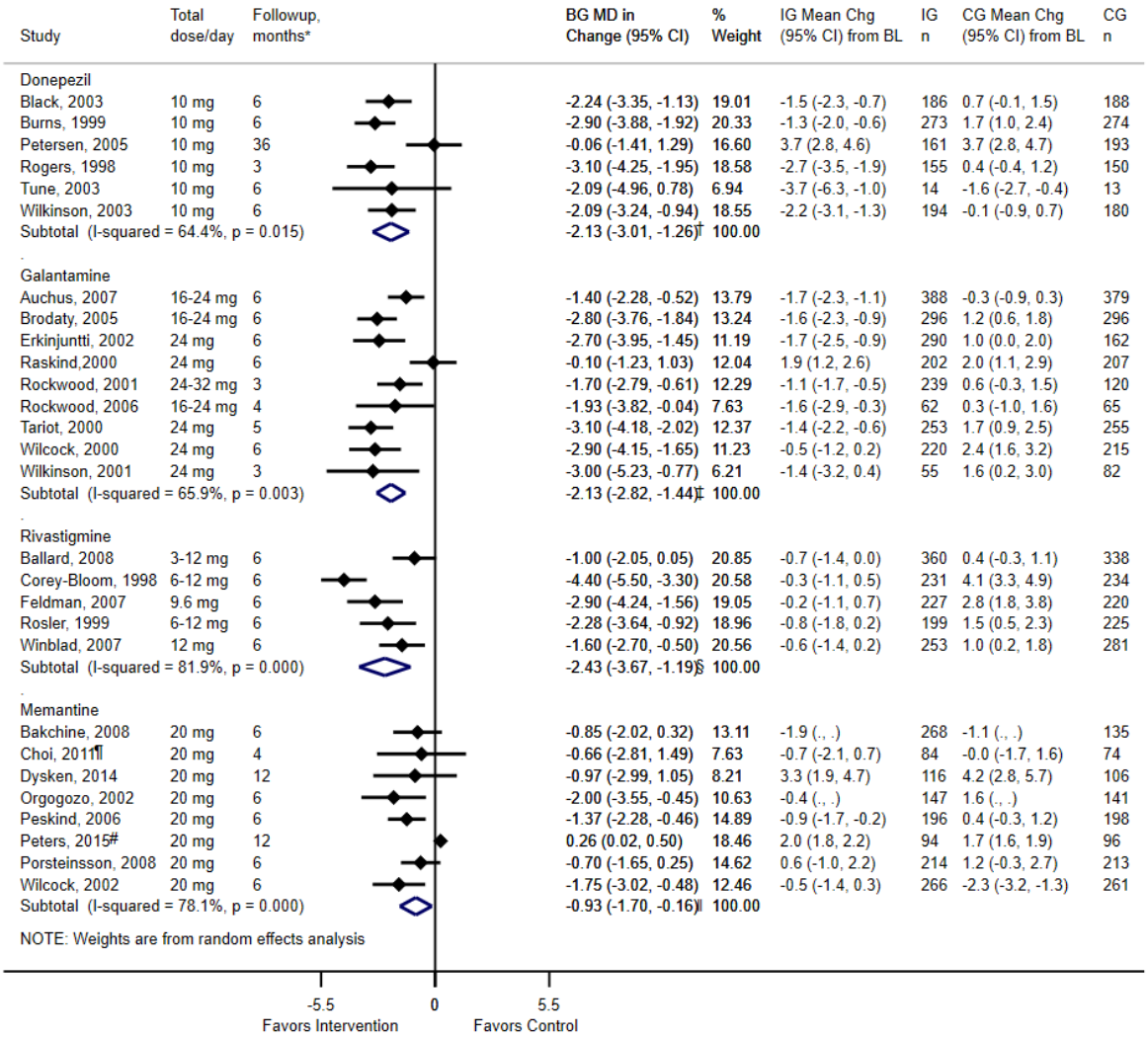
Figure 8. Test Accuracy of Longer, Self-Administered Tests (KQ 2)



* Short IQCODE

Abbreviations: CAMCI = Computer Assessment of Mild Cognitive Impairment; CAST = Cognitive Assessment Screening Test; CI = confidence interval; CIDS = Concord Informant Dementia Scale; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; IQCODE-Short = Informant Questionnaire on Cognitive Decline in the Elderly - short version; MCI = mild cognitive impairment; NA = not applicable; SCIDS = Short Concord Informant Dementia Scale

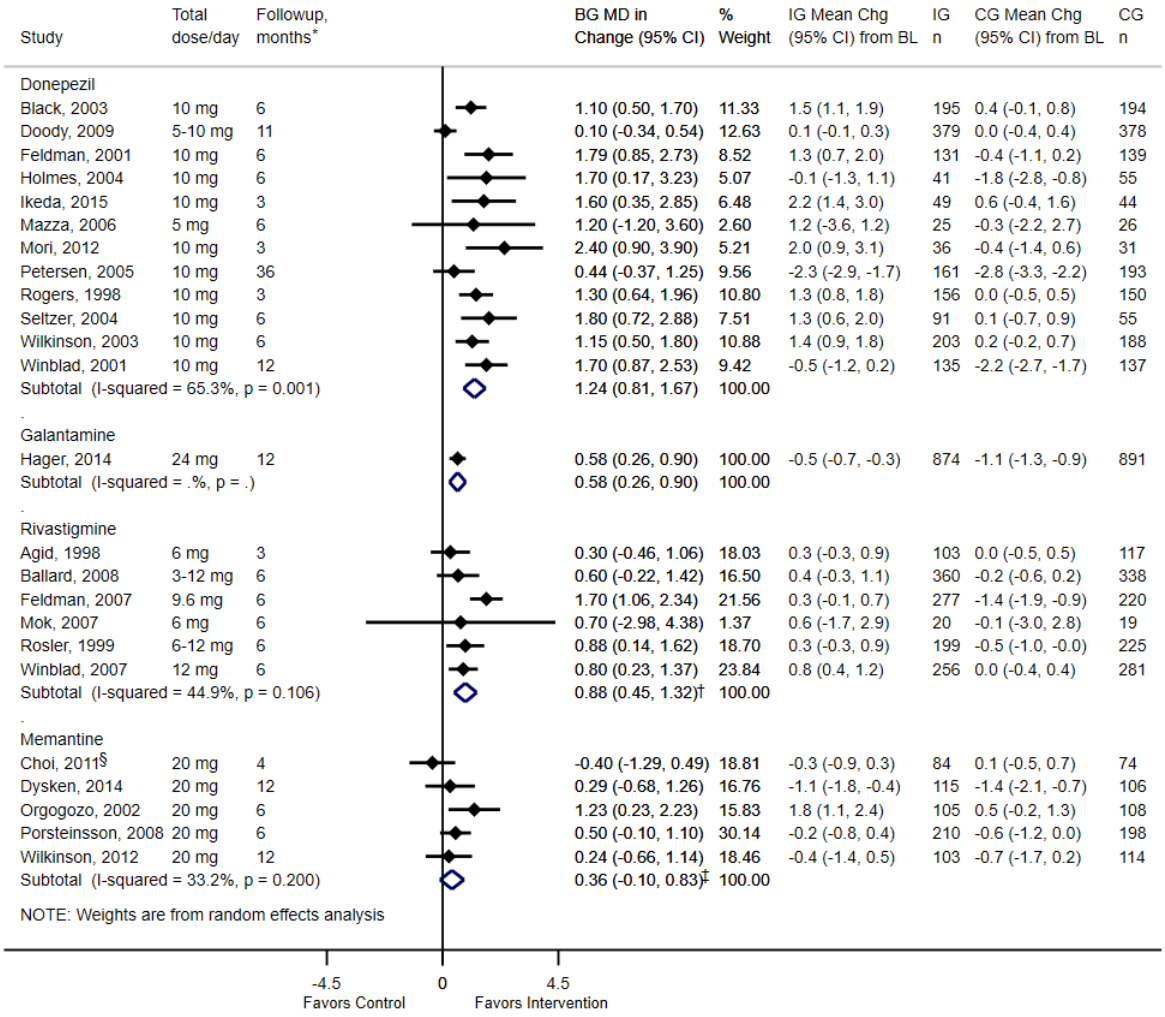
Figure 9. Pooled Analysis of Change in Global Cognitive Function (Measured by ADAS-Cog-11) (KQ4), AChEIs and Memantine Compared With Placebo, by Medication Type



* For all analyses, we focused on 6- to 12-month outcomes and included only shorter- or longer-term results when 6- or 12-month outcomes were not available.
† Pooled mean difference, -2.13 (95% CI: -3.32 to -0.94); k=6; n=1981; I^2=64.4%, based on restricted maximum likelihood method with Knapp-Hartung modification
‡ Pooled mean difference, -2.13 (95% CI: -2.94 to -1.32); k=9; n=3786; I^2=65.9%, based on restricted maximum likelihood method with Knapp-Hartung modification
§ Pooled mean difference, -2.43 (95% CI: -4.10 to -0.75); k=5; n=2618; I^2=81.9%, based on restricted maximum likelihood method with Knapp-Hartung modification
‖ Pooled mean difference, -0.88 (95% CI: -1.65 to -0.11); k=8; n=2609; I^2=78.1%, based on restricted maximum likelihood method with Knapp-Hartung modification
¶ Both intervention and control groups received 5-10 mg/day rivastigmine plus memantine or placebo
# Both intervention and control groups received 24 mg/day galantamine plus memantine or placebo

Abbreviations: AChEIs = acetylcholinesterase inhibitors; ADAS-Cog-11 = Alzheimer's disease assessment scale–cognitive subscale (11-items); BG = between-group; BL = baseline; CG = control group; Chg = change; CI = confidence interval; IG = intervention group; KQ = key question; MD = mean difference; mg = milligrams; n = sample size

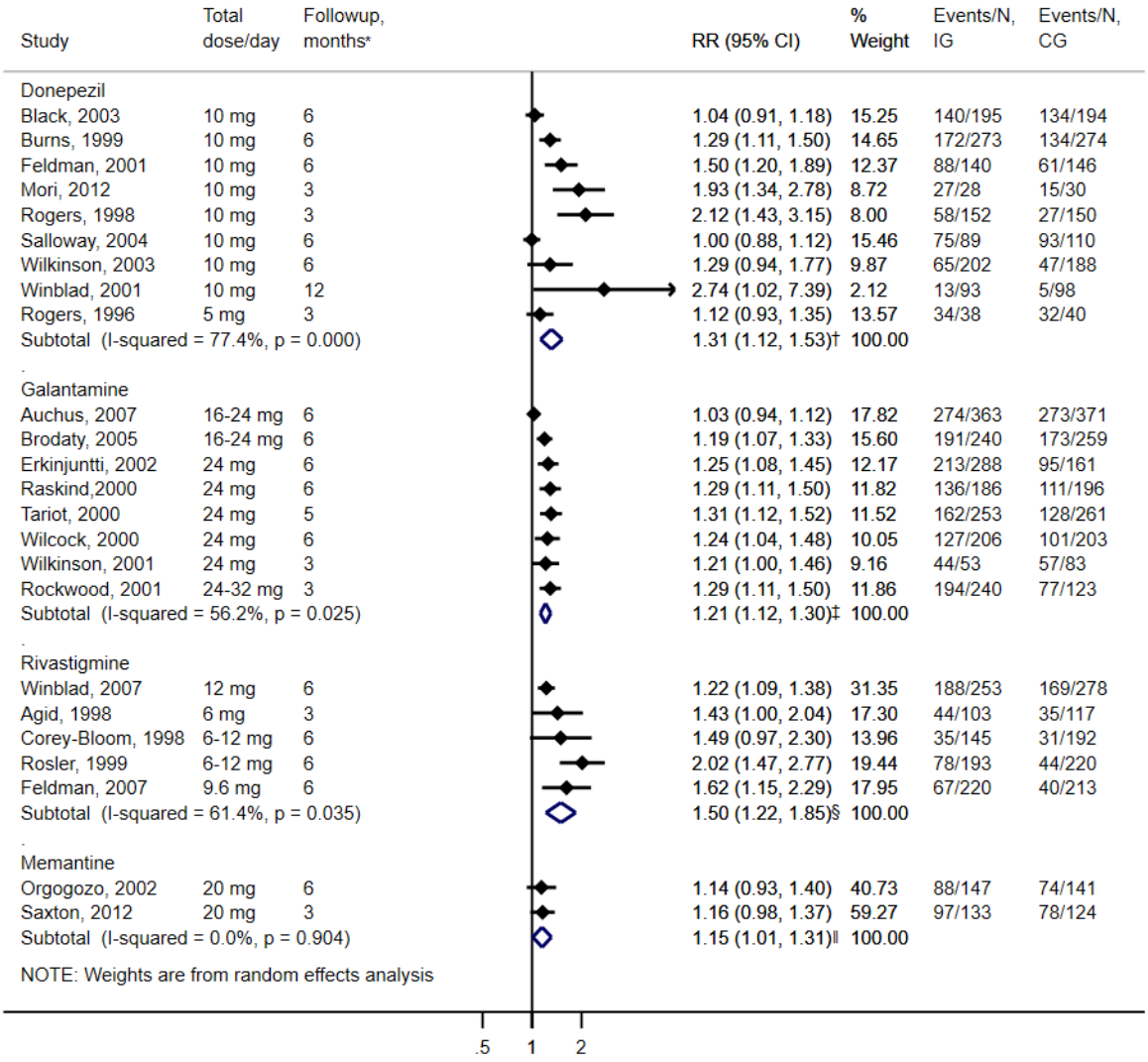
Figure 10. Pooled Analysis of Change in Global Cognitive Function (Measured by MMSE) (KQ4), AChEIs and Memantine Compared With Placebo, by Medication Type



* For all analyses, we focused on 6- to 12-month outcomes and included only shorter- or longer-term results when 6- or 12-month outcomes were not available.
† Pooled mean difference, 0.88 (95% CI: 0.28 to 1.49); k=6; n=2415; I^2=44.9%, based on restricted maximum likelihood method with Knapp-Hartung modification
‡ Pooled mean difference, 0.36 (95% CI: -0.31 to 1.04); k=5; n=1217; I^2=33.2%, based on restricted maximum likelihood method with Knapp-Hartung modification
§ Both intervention and control groups received 5-10 mg/day rivastigmine plus memantine or placebo

Abbreviations: AChEIs = acetylcholinesterase inhibitors; BG = between-group; BL = baseline; CG = control group; Chg = change; CI = confidence interval; Intv = Intervention; IG = intervention group; KQ = key question; MD = mean difference; mg = milligrams; MMSE = mini-mental state examination; n = sample size

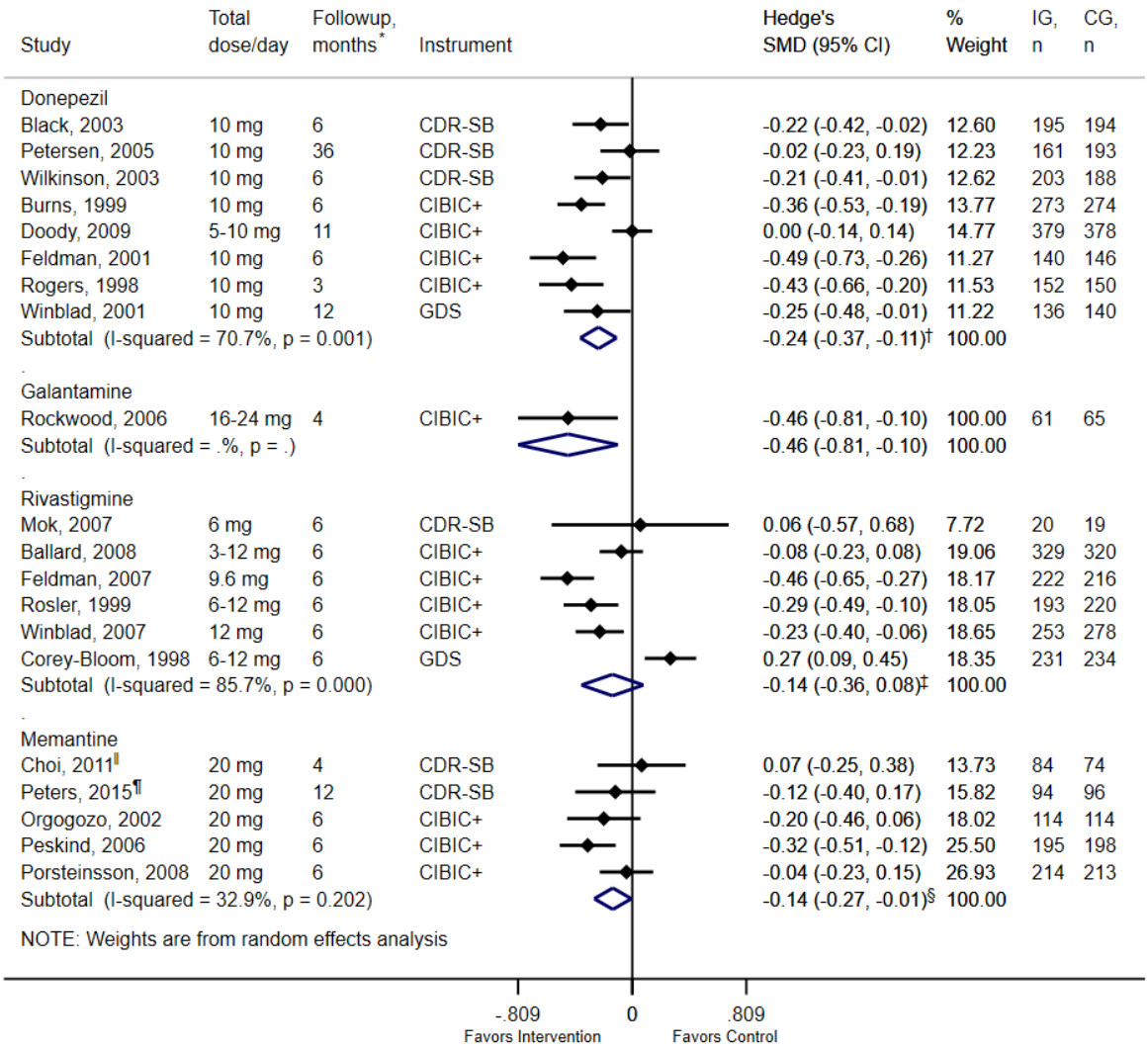
Figure 11. Pooled Analysis of Risk of Improvement or Maintenance in Global Function (KQ4), AChEIs and Memantine Compared With Placebo, by Medication Type



* For all analyses, we focused on 6- to 12-month outcomes and included only shorter- or longer-term results when 6- or 12-month outcomes were not available.
† Pooled mean difference, 1.33 (95% CI: 1.07 to 1.66); k=9; n=2440; I^2=77.4%, based on restricted maximum likelihood method with Knapp-Hartung modification
‡ Pooled mean difference, 1.21 (95% CI: 1.11 to 1.31); k=8; n=3486; I^2=56.2%, based on restricted maximum likelihood method with Knapp-Hartung modification
§ Pooled mean difference, 1.49 (95% CI: 1.13 to 1.98); k=5; n=1934; I^2=61.4%, based on restricted maximum likelihood method with Knapp-Hartung modification
‖ Pooled mean difference, 1.15 (95% CI: 0.49 to 2.69); k=2; n=545; I^2=0.0%, based on restricted maximum likelihood method with Knapp-Hartung modification

Abbreviations: AChEIs = acetylcholinesterase inhibitors; CG = control group; CI = confidence interval; IG = intervention group; KQ = key question; RR = risk ratio; mg = milligrams; N = sample size

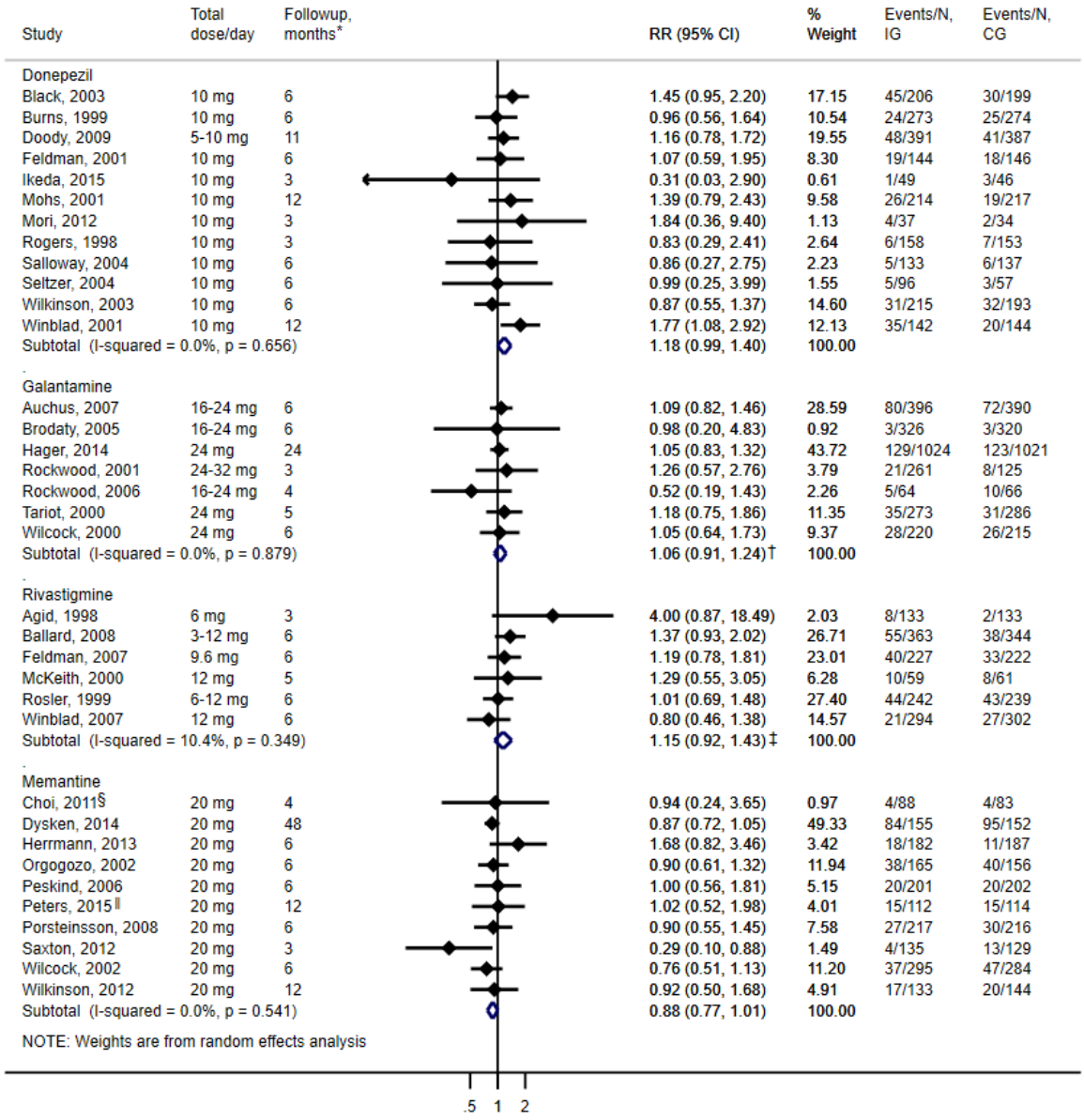
Figure 12. Pooled Analysis of Change in Global Function (Standardized Mean Difference) (KQ4), AChEIs and Memantine Compared With Placebo, by Medication Type



* For all analyses, we focused on 6- to 12-month outcomes and included only shorter- or longer-term results when 6- or 12-month outcomes were not available.
† Pooled mean difference, -0.24 (95% CI: -0.39 to -0.09); k=8; n=3302; I^2=70.7%, based on restricted maximum likelihood method with Knapp-Hartung modification
‡ Pooled mean difference, -0.14 (95% CI: -0.43 to 0.15); k=6; n=2535; I^2=85.7%, based on restricted maximum likelihood method with Knapp-Hartung modification
§ Pooled mean difference, -0.14 (95% CI: -0.33 to 0.05); k=5; n=1396; I^2=32.9%, based on restricted maximum likelihood method with Knapp-Hartung modification which resulted to no statistical significance
‖ Both intervention and control groups received 5-10 mg/day rivastigmine plus memantine or placebo
¶ Both intervention and control groups received 24 mg/day galantamine plus memantine or placebo

Abbreviations: AChEIs = acetylcholinesterase inhibitors; BL = baseline; CG = control group; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; CI = confidence interval; CIBIC+ = Clinician's Interview-Based Impression of Change with caregiver's input; GDS = Global Deterioration Scale; IG = intervention group; KQ = key question; SMD = standardized mean difference; mg = milligrams; n = sample size

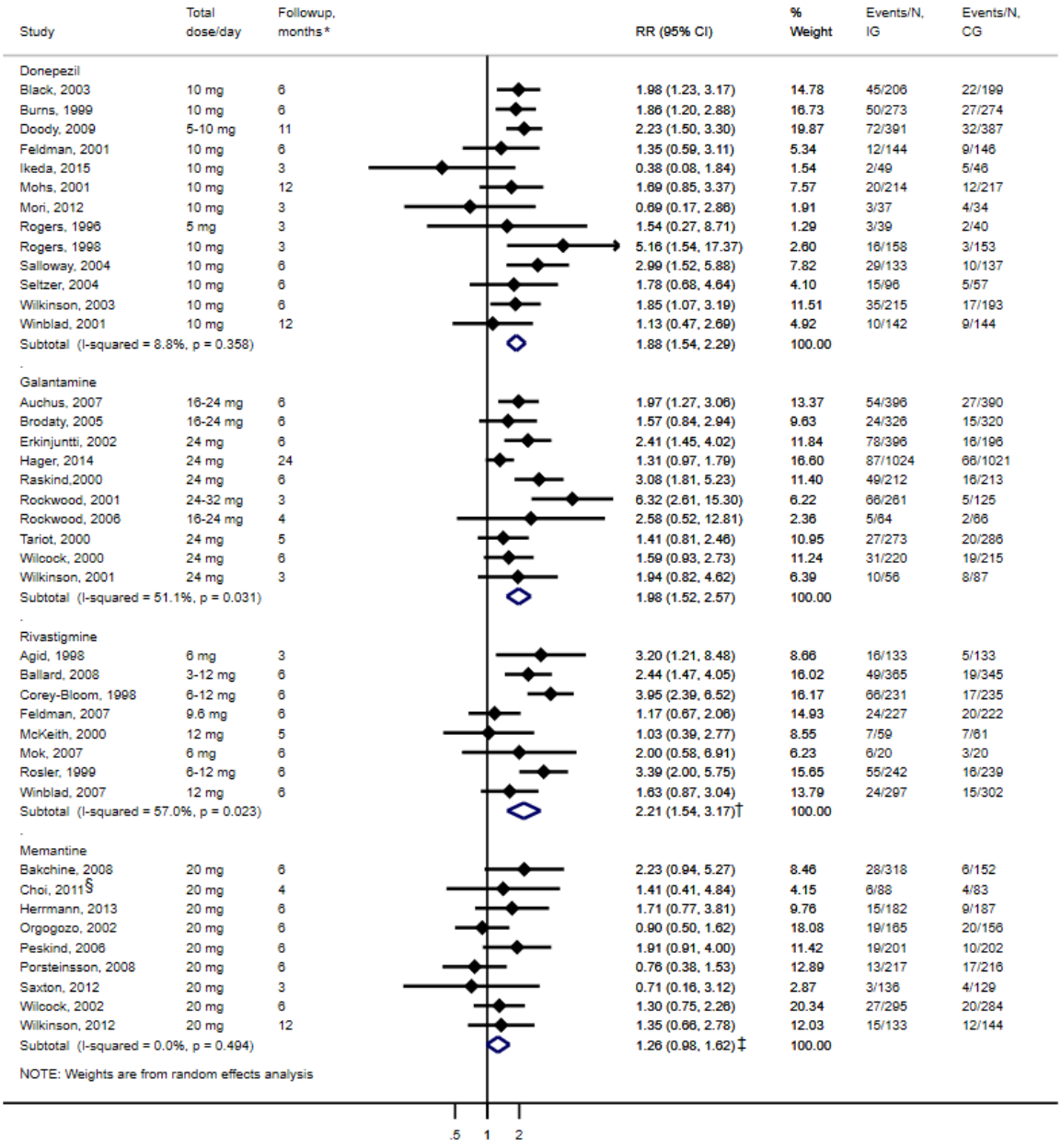
Figure 13. Pooled Analysis of Risk of Serious Adverse Events (KQ5), AChEIs and Memantine Compared With Placebo, by Medication Type



* Followup was at the end of trial.
† Pooled mean difference, 1.06 (95% CI: 0.88 to 1.29); k=7; n=4987; I^2=0.0%, based on restricted maximum likelihood method with Knapp-Hartung modification
‡ Pooled mean difference, 1.15 (95% CI: 0.87 to 1.52); k=6; n=2619; I^2=10.4%, based on restricted maximum likelihood method with Knapp-Hartung modification
§ Both intervention and control groups received 5-10 mg/day rivastigmine plus memantine or placebo
‖ Both intervention and control groups received 24 mg/day galantamine plus memantine or placebo

Abbreviations: AChEIs = acetylcholinesterase inhibitors; CG = control group; CI = confidence interval; IG = intervention group; Intv = intervention; KQ = key question; RR = risk ratio; mg = milligrams; N = sample size

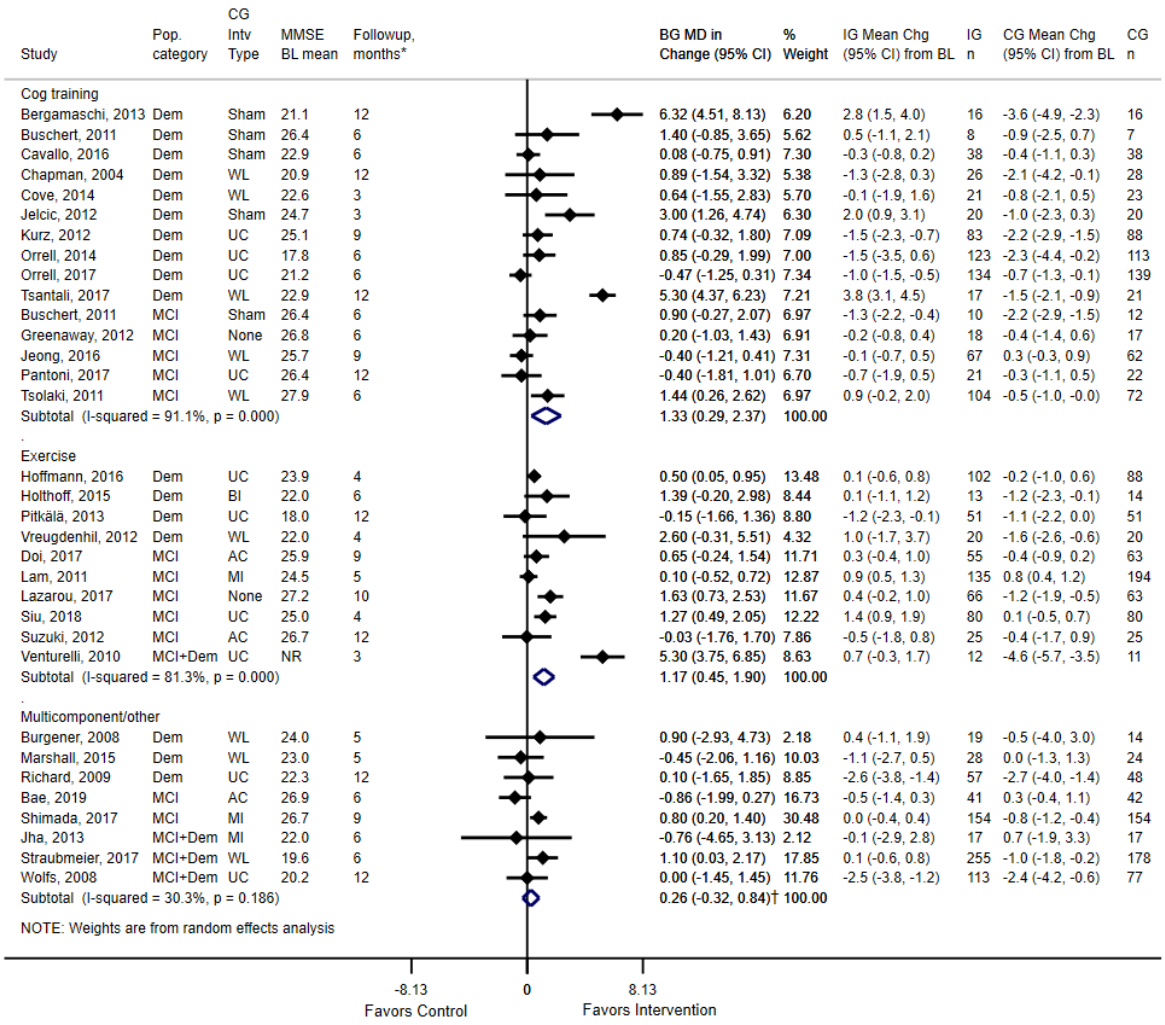
Figure 14. Pooled Analysis of Risk of Withdrawals Due to Adverse Events (KQ5), AChEIs and Memantine Compared With Placebo, by Medication Type



* Followup was at the end of trial.
† Pooled mean difference, 2.21 (95% CI: 1.43 to 3.42); k=8; n=3131; I^2=57.0% based on restricted maximum likelihood method with Knapp-Hartung modification
‡ Pooled mean difference, 1.26 (95% CI: 0.94 to 1.70); k=9; n=3288; I^2=0.0%, based on restricted maximum likelihood method with Knapp-Hartung modification
§ Both intervention and control groups received 5-10 mg/day rivastigmine plus memantine or placebo

Abbreviations: AChEIs = acetylcholinesterase inhibitors; CG = control group; CI = confidence interval; IG = intervention group; Intv = intervention; KQ = key question; RR = risk ratio; mg = milligrams; N = sample size

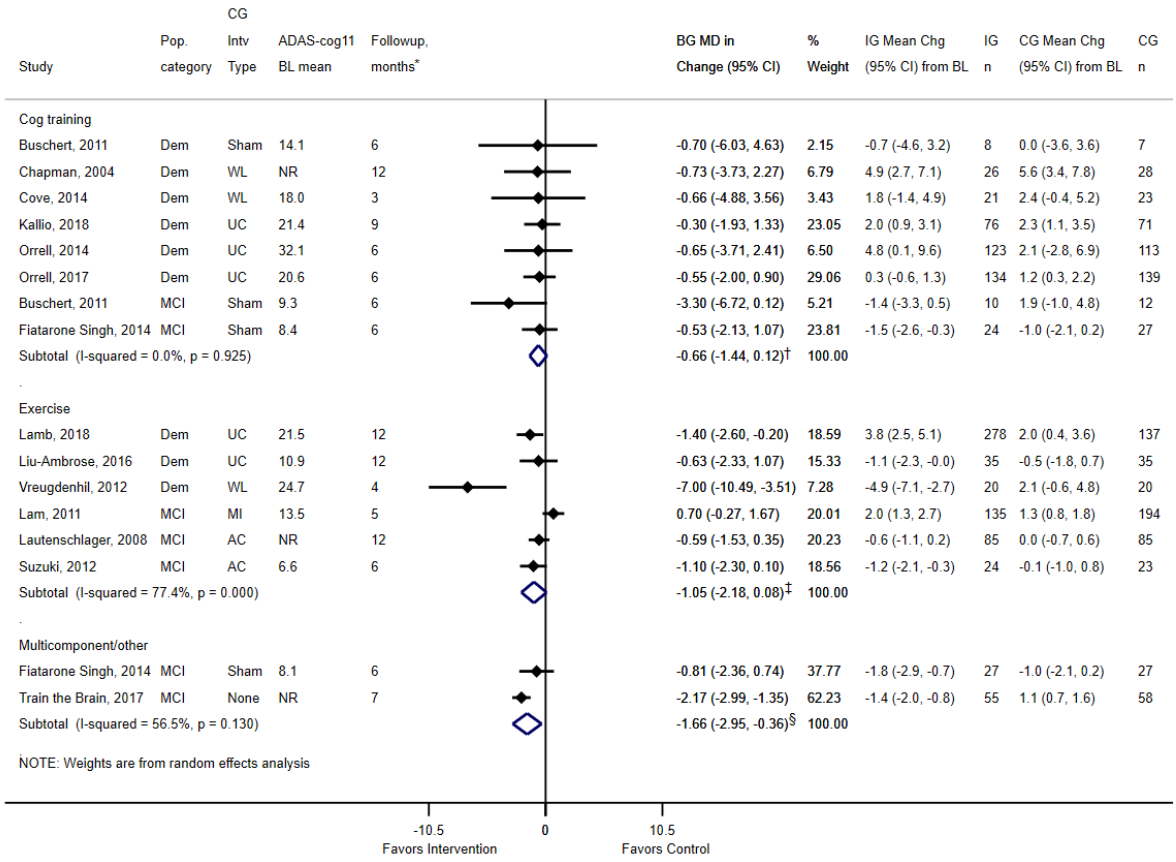
Figure 15. Pooled Analysis of Change in Global Cognitive Function (Measured by MMSE) (KQ4), Patient-Level Nonpharmalogic Interventions Compared With Controls, by Intervention Type



* For all analyses, we focused on 6- to 12-month outcomes and included only shorter- or longer-term results when 6- or 12-month outcomes were not available.
† Pooled mean difference, 0.26 (95% CI: -0.54 to 1.00); k=8; n=1238; I^2=30.3%, based on restricted maximum likelihood method with Knapp-Hartung modification which resulted to no statistical significance

Abbreviations: AC = attention control; BI = brief intervention; BG = between-group; BL = baseline; CG = control group; Chg = change; CI = confidence interval; Dem = dementia; Intv = Intervention; IG = intervention group; KQ = key question; MCI = mild cognitive impairment; MD = mean difference; MI = minimal intervention; MMSE = mini-mental state examination; n = sample size; NR = not reported; Pop = population; UC = usual care; WL = waitlist

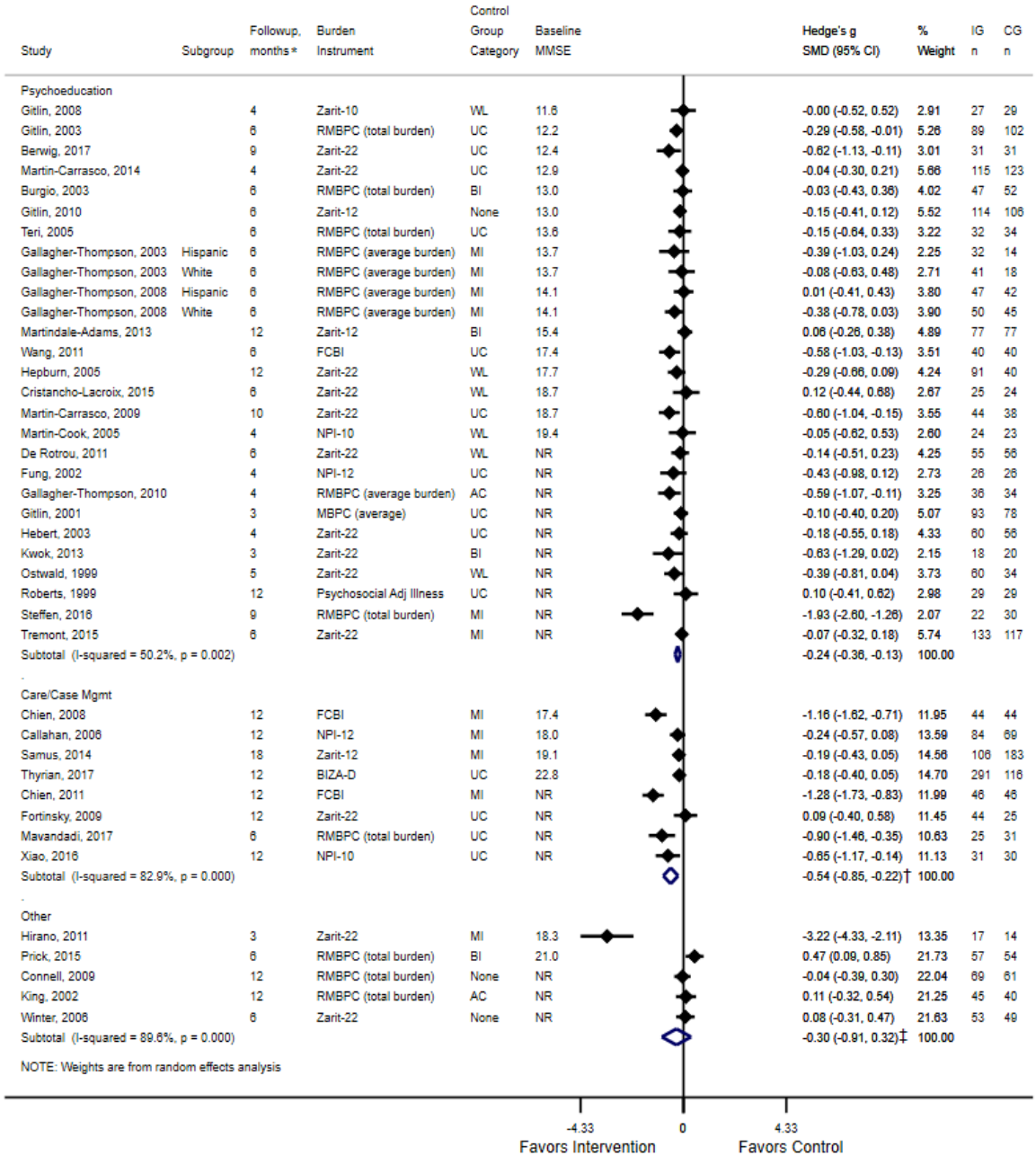
Figure 16. Pooled Analysis of Change in Global Cognitive Function (Measured by ADAS-Cog-11) (KQ4), Patient-Level Nonpharmalogic Interventions Compared With Controls, by Intervention Type



* For all analyses, we focused on 6- to 12-month outcomes and included only shorter- or longer-term results when 6- or 12-month outcomes were not available.
†Pooled mean difference, -0.66 (95% CI: -1.60 to 0.29); k=8; n=842; I^2=0.0%, based on restricted maximum likelihood method with Knapp-Hartung modification
‡ Pooled mean difference, -1.05 (95% CI: -3.49 to 1.10); k=6; n=1071; I^2=77.4%, based on restricted maximum likelihood method with Knapp-Hartung modification
§ Pooled mean difference, -1.66 (95% CI: -10.03 to 6.72); k=2; n=167; I^2=56.5%, based on restricted maximum likelihood method with Knapp-Hartung modification

Abbreviations: AC = attention control; ADAS-Cog-11 = Alzheimer's disease assessment scale–cognitive subscale (11-items); BI = brief intervention; BG = between-group; BL = baseline; CG = control group; Chg = change; CI = confidence interval; Dem = dementia; Intv = Intervention; IG = intervention group; KQ = key question; MCI = mild cognitive impairment; MD = mean difference; MI = minimal intervention; n = sample size; NR = not reported; Pop = population; UC = usual care; WL = waitlist

Figure 17. Pooled Analysis of Change in Caregiver Burden (Standardized Mean Difference) (KQ4), Caregiver and Caregiver-Patient Dyad Interventions Compared With Controls, by Intervention Type



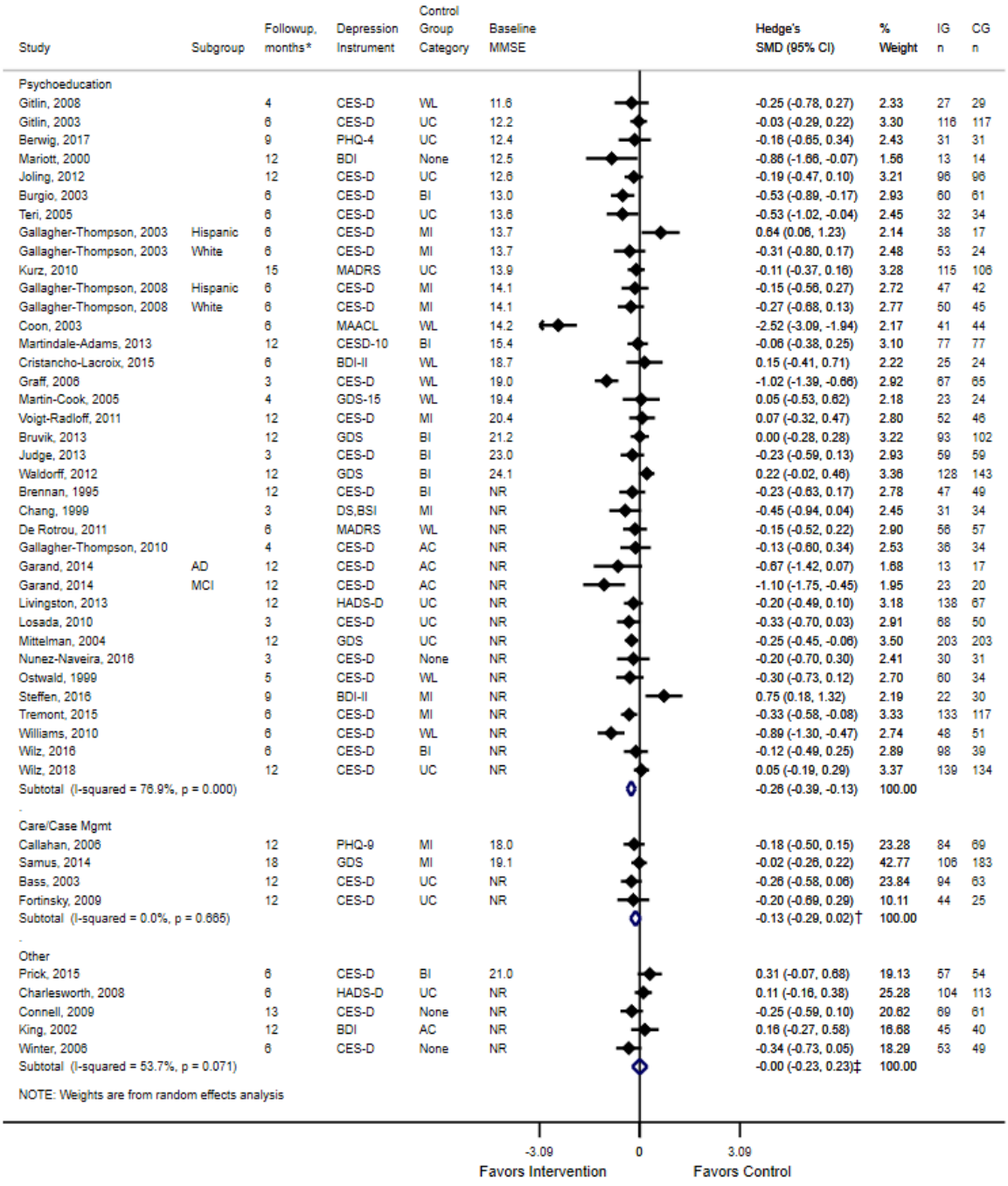
* For all analyses, we focused on 6- to 12-month outcomes and included only shorter- or longer-term results when 6- or 12-month outcomes were not available.
† Pooled mean difference, -0.54 (95% CI: -0.96 to -0.12); k=8; n=1215; I^2=82.9%, based on restricted maximum likelihood method with Knapp-Hartung modification
‡ Pooled mean difference, -0.45 (95% CI: -2.26 to 1.36); k=5; n=459; I^2=89.6%, based on restricted maximum likelihood method with Knapp-Hartung modification

Abbreviations: AC = attention control; BI = brief intervention; BIZA-D = Berlin Inventory of Caregivers' Burden with Dementia; BG = between-group; BL = baseline; CG = control group; CI = confidence interval; Dem = dementia; FCBI = Family Caregiving Burden Inventory; IG = intervention group; KQ = key question; MCI = mild cognitive impairment; MBPC = Memory and Behavior Checklist; Mgmt = management; MI = minimal intervention; MMSE = mini-mental state examination; n = sample

Figure 17. Pooled Analysis of Change in Caregiver Burden (Standardized Mean Difference) (KQ4), Caregiver and Caregiver-Patient Dyad Interventions Compared With Controls, by Intervention Type

size; NPI-10 = Neuropsychiatric Inventory-10 item; NPI-12 = Neuropsychiatric Inventory-12 item; NR = not reported; Psychosocial Adj Illness = Psychosocial Adjustment to Illness scale; RMBPC = Revised Memory and Behavior Checklist; SMD = standardized mean difference; UC = usual care; WL = waitlist; Zarit-10 = Zarit Burden Interview-10 item; Zarit-22 = Zarit Burden Interview-22 item

Figure 18. Pooled Analysis of Change in Caregiver Depression (Standardized Mean Difference) (KQ4), Caregiver and Caregiver-Patient Dyad Interventions Compared With Controls, by Intervention Type



* For all analyses, we focused on 6- to 12-month outcomes and included only shorter- or longer-term results when 6- or 12-month outcomes were not available.
† Pooled mean difference, -0.13 (95% CI: -0.39 to 0.12); k=4; n=668; I^2=0.0%, based on restricted maximum likelihood method with Knapp-Hartung modification
‡ Pooled mean difference, -0.0 (95% CI: -0.34 to 0.34); k=5; n=645; I^2=53.7%, based on restricted maximum likelihood method with Knapp-Hartung modification

Abbreviations: AC = attention control; AD = Alzheimer's disease; BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory – Second Edition; BI = brief intervention; BG = between-group; BL = baseline; CES-D = Center for

Figure 18. Pooled Analysis of Change in Caregiver Depression (Standardized Mean Difference) (KQ4), Caregiver and Caregiver-Patient Dyad Interventions Compared With Controls, by Intervention Type

Epidemiologic Studies – Depression; CES-D-10 = 10-item Center for Epidemiologic Studies – Depression; CG = control group; CI = confidence interval; Dem = dementia; DS, BSI = Brief Symptom Inventory – Depression subscale; GDS = Geriatric Depression Scale; GDS-15 = Geriatric Depression Scale-15 item; HADS-D = Hospital Anxiety and Depression Scale; IG = intervention group; KQ = key question; MAACL = Multiple Affect Adjective Checklist; MADRS = Montgomery Asberg Depression Rating Scale; MCI = mild cognitive impairment; Mgmt = management; MCI = mild cognitive impairment; MI = minimal intervention; MMSE = mini-mental state examination; n = sample size; NR = not reported; PHQ-9 = Patient Health Questionnaire-9; SMD = standardized mean difference; UC = usual care; WL = waitlist

Table 1. Recommendations From Other Organizations

Organization	Year	Recommendation Statement
U.S. Department of Veterans Affairs[96]	2016	Recommends against routine screening for cognitive impairment in persons of any age. Veteran's Health Administration Clinicians should use dementia warning signs to prompt assessment of cognitive function. If warning signs are present, patients should be evaluated further.
Canadian Task Force on Preventive Health Care (CTFPHC)[93]	2016	Recommends against screening asymptomatic older adults (≥65 years) for cognitive impairment (Strong recommendation, low-quality evidence)
Gerontological Society of America (GSA)[98]	2015	Recommends that primary care providers routinely ask beneficiaries about any noticeable changes in memory of cognition that have occurred since previous office visits during the Medicare Annual Wellness Visit (AWV). Additionally, primary care providers should use their clinical judgment and observational skills to determine whether any changes in memory or cognition since previous encounters with beneficiaries are noticeable during the Medicare AWV.
International Association of Gerontology and Geriatrics (IAGG)[456]	2015	Recommends screening to identify early cognitive impairment among individuals with known risk factors for dementia (e.g., subjective cognitive concerns or family history of dementia)
Alzheimer's Association[97, 102]	2013	Recommends screening for cognitive impairment among: • Individuals with memory concerns or other cognitive complaints. Non-memory triggers include personality change, depression, deterioration of chronic disease without explanation, and falls or balance issues • Informant reports of cognitive impairment, with or without patient concurrence • Medicare beneficiaries, as part of the Annual Wellness Visit
National Institute for Health Care and Excellence (NICE)[457]	2011	Recommends against screening for dementia in general population.
Royal Australian College of General Practitioners (RACGP)[95]	2012	Found no evidence of benefit from screening for dementia in adults over age 65 without symptoms. Symptoms and signs of dementia should be detected opportunistically and assessed using questions addressed to the person and/or their caregiver.
European Federation of Neurological Societies (EFNS)[94]	2010	No recommendations for general, asymptomatic populations.

Table 2. Study and Population Characteristics of Included Diagnostic Accuracy Studies (KQ 2)

Author, year Quality	Country; recruitment setting	N Screened	Dem, %	MCI, %	Age, mean (range)	Female, %	Race/ Ethnicity, %	SES	Diagnostic Criteria	Reference Standard
Ayalon, 2011[124] Fair	US; Community-based	647	32	29	79 (≥70)	51	NR	Mean edu, years: 11.8	Dementia: NA MCI: Defined as functional impairment per respondent or informant report that did not meet criteria for dementia on neuropsychological measures that was below expectations and ≥1.5 SD below published norms.	Neuropsychological battery, self-report depression measure, standardized neurologic examination, physiological testing, and genetic testing
Ball, 2001[125] Fair	US; Community-based	170 (53 in analysis)	9	NR	76 (≥65)	100	NR	Mean edu, years: 13.6	Dementia: NINCDS-ADRDA MCI: NA	Short Blessed Test, clinical examination, and neuropsychological test battery
Borson, 2006[126] Fair	US; Community-based	371	42	21	NR (NR)	NR	White: 7 Black: 17 Asian: 48 Hispanic: 7 Other: 6	NR	Dementia: CDR≥1 MCI: CDR=0.5	Neuropsychological test battery, informant interview, medical history and examination
Brodaty, 2002*[127] Fair	AUS; Primary care	283	29	NR	80 (56-94)	59	NR	% ≤8 years edu: 44.2 % >8 years edu: 55.8	Dementia: DSM-IV MCI: NA	Neuropsychological testing
Buschke, 1999[128] Fair	US; Community-based, Primary care	483	10	NR	80 (≥65)	64	White: 80.7 Black: 16.2 Other: 2.7	Mean edu, years: 12.1	Dementia: DSM-III-R MCI: NA	Neuropsychological test battery
Callahan, 2002[129] Fair	US; Community-based	344	4	22	74 (65-99)	59	Black: 100	Mean (range) edu, years: 10.4 (0-16)	Dementia: NR MCI: NR	Physical examination and neurologic examination
Chan, 2016[130†] Fair	SGP; Primary care	309	24	NR	72 (≥60)	54	Asian: 99	Mean edu, years: 7.93	Dementia: DSM-IV, CDR MCI: NA	Clinical assessment and neuropsychological test battery

Table 2. Study and Population Characteristics of Included Diagnostic Accuracy Studies (KQ 2)

Author, year Quality	Country; recruitment setting	N Screened	Dem, %	MCI, %	Age, mean (range)	Female, %	Race/ Ethnicity, %	SES	Diagnostic Criteria	Reference Standard
Cook, 2009[131‡] Fair	US; Community-based, Other medical	71	0	24	75 (≥65)	56	White: 93	Mean edu, years: 16.1	Dementia: NA MCI: NR	Neuropsychological test battery
Cruz-Orduna, 2012[132‡] Fair	ESP; Primary care	160	9	47	72 (>49)	70	NR	Edu, %: None/Incomplete: 44.4	Dementia: Performance < 10th percentile in memory and at least one other domain, cognitive deterioration considered the cause of impairment in function, and confusion state not present. MCI: Performance < 10th percentile in at least 1 test	Neuropsychological test battery
Cullen, 2005[133] Fair	IRL; Primary care	1115	4	5	75 (≥65)	68	NR	Mean edu, years: 9.9	Dementia: NR MCI: NR	GMS-AGECAT (diagnostic interview)
Cummings-Vaughn, 2014[134†] Good	US; Other medical	136	21	42	79 (66-95)	2	NR	Completed HS: 41%	Dementia: CDR MCI: CDR	CDR
Del Ser, 2006[135] Fair	ESP; Community-based	416	12	NR	79 (>65)	52	NR	% No Formal edu: 25	Dementia: NR MCI: NA	Neuropsychological test battery
Donnelly, 2008[136] Fair	US; Primary care	100	NR	20	78 (65-89)	1	White: 95 Black: 4 AI/AN: 1	Mean edu, years: 12.9	Dementia: NA MCI: ≥1 SD below the normative mean	Dementia Rating Scale
Ehreke, 2009[138] Fair	DEU; Primary care	3198	0	14	80 (≥75)	65	NR	Level of edu: % Low: 61.8 % Middle: 27.5 % High: 10.7	Dementia: NA MCI: Winblad	SIDAM

Table 2. Study and Population Characteristics of Included Diagnostic Accuracy Studies (KQ 2)

Author, year Quality	Country; recruitment setting	N Screened	Dem, %	MCI, %	Age, mean (range)	Female, %	Race/ Ethnicity, %	SES	Diagnostic Criteria	Reference Standard
Ehreke, 2011[137] Fair	DEU; Community-based	428	0	14	83 (≥75)	73	NR	% Low edu: 63.5 % Assisted Living/Residential Care: 11.3 in institutional care	Dementia: NA MCI: International Working Group on MCI (Winblad, 2004) - (a) absence of dementia according to DSM-IV or ICD-10; (b) evidence of cognitive decline: subjective cognitive impairment (measured by self-rating or informant report)	SIDAM
Erkinjuntti, 1987[139] Fair	FIN; Community-based	119	2	NR	73 (65-84)	65	NR	% Grade school or less: 85 % Assisted Living/Residential Care: 4	Dementia: NR MCI: NA	Neuropsychological test battery and medical history
Fillenbaum, 1990[140] Fair	US; Community-based	164	16	NR	NR (≥65)	58	White: 49.4 Black: 50.6	NR	Dementia: DSM-III and NINCDS/ADRDA MCI: NA	Semi-structured interview, including a modified physical and neurological examination
Fong, 2011[141] Fair	US; Community-based	709	12	NR	79 (≥70)	60	White: 91	NR	Dementia: DSM-III MCI: NA	Functional status, health information, neuropsychological examination
Fuchs, 2012[142] Fair	DEU; Primary care	423	5	NR	82 (75-89)	68	NR	% Low level of edu: 62.2	Dementia: DSM-IV and NINCDS/ADRDA MCI: NA	Neuropsychological test battery, medical and family history, drug inventory, SES, lifestyle, and GDS
Gagnon, 1990[143] Fair	FRA; Community-based	2730	4	NR	75 (≥65)	59	NR	% No edu/Grade School: 66	Dementia: DSM-III MCI: NA	Psychometric tests

Table 2. Study and Population Characteristics of Included Diagnostic Accuracy Studies (KQ 2)

Author, year Quality	Country; recruitment setting	N Screened	Dem, %	MCI, %	Age, mean (range)	Female, %	Race/ Ethnicity, %	SES	Diagnostic Criteria	Reference Standard
Galvin, 2005[144] Fair	US; Community-based, Primary care, Other medical	236	24	29	78 (55-102)	53	NR	NR	Dementia: DSM-IV and NINCDS/ADRDA MCI: CDR=0.5	Semistructured interview
Grut, 1993[145] Fair	SWE; Community-based	1810	14	NR	NR (≥75)	76	NR	% Elementary edu: 52.9	Dementia: DSM-III-R MCI: NA	Clinical examination, family interview, and laboratory tests
Heun, 1998[146] Fair	DEU; Community-based	291	13	NR	77 (60-99)	60	NR	Mean edu, years: 9.5	Dementia: DSM-III-R MCI: NA	CIDI and SIDAM
Holsinger, 2012[147] Good	US; Primary care	639	3	39	75 (≥65)	7	White: 73 Black: 26 Hispanic: 1 Other: <1	Mean edu, years: 13.0	Dementia: DSM-IV, NINCDS-ADRDA, NINDS-AIREN MCI: Functional impairment due to cognitive impairment that the participant or informant reported that did not meet criteria for dementia (that was fairly mild), and or performance on neuropsychological measure	Clinical interviews, neuropsychological testing, neurological examination, and review of electronic medical records
Hooijer, 1992[148] Fair	NLD; Primary care	358	4	NR	NR	NR	NR	NR	Dementia: GMS, AGECAT MCI: NA	GMS-AGECAT
Hsu, 2015[149†] Good	TWN; Community-based	276	6	NR	68 (≥60)	51	NR	Mean edu, years: 11.4	Dementia: DSM-IV MCI: NA	Neurological examination, function, laboratory tests, imaging
Jeong, 2004[150] Good	KOR; Community-based	235	20	23	74 (NR)	66	NR	Median edu, years: 1	Dementia: DSM-IV, NINCDS-ADRDA MCI: DSM-IV (people with cognitive decline	Clinical exam and neuropsychiatric inventory

Table 2. Study and Population Characteristics of Included Diagnostic Accuracy Studies (KQ 2)

Author, year Quality	Country; recruitment setting	N Screened	Dem, %	MCI, %	Age, mean (range)	Female, %	Race/ Ethnicity, %	SES	Diagnostic Criteria	Reference Standard
									who did not meet DSM-IV criteria for dementia)	
Jorm, 1996[151] Fair	AUS; POWs/ex-servicemen	144	NR	NR	73 (66-83)	0	NR	NR	Dementia: ICD-9 MCI: NR	Neuropsychological test battery
Juva, 1997[152] Fair	FIN; Community-based	656	14	NR	80 (75-85)	73	NR	Low edu: 74.4%	Dementia: DSM III-R MCI: NA	CDR followed by a clinical assessment when indicated
Kahle-Wrobleski, 2007[153] Fair	US; Community-based	435	36	28	95 (90-104)	74	NR	>12 years of formal edu: 73%	Dementia: DSM-IV MCI: NR	Neurological examination
Kaufer, 2008[154] Fair	US; Other medical	146	38	52	83 (≥65)	79	White: 90	12 years of edu or less: 55%	Dementia: DSM-IV MCI: DSM-IV	Neuropsychological testing, physical examination, and neurologic examination
Kay, 1985[155] Fair	AUS; Electoral roll	274	14	NR	NR (≥70)	64	NR	NR	Dementia: DSM-III MCI: NA	GMS-6
Kirby, 2001[156] Fair	IRL; Primary care	648	6	NR	75 (≥65)	NR	NR	Mean edu, years: 10.8	Dementia: GMS MCI: NA	GMS-AGECAT (diagnostic interview)
Kuslansky, 2002[157] Fair	US; Community-based, Other medical	240	12	NR	79 (>70)	64	White: 72 Black: 28	Mean edu, years: 12.5	Dementia: DSM-III-R; DSM-IV; NINCDS-ADRDA MCI: NA	Medical and social history, neurological examination, neuropsychological testing
Lam, 2008[158] Fair	HKG; Community-based	459	10	35	71 (NR)	54	Asian: 100	Mean edu, years: 4.8	Dementia: NINCDS-ADRDA MCI: NR	CDR
Lee, 2008[159] Fair	KOR; Community-based, Hospital	196	22	19	70 (≥65)	65	Asian: 100	<6 years edu: 53.1%	Dementia: NR MCI: NR	Neuropsychological test battery
Lee, 2008[160] Fair	KOR; Other medical	465	0	48	71 (≥60)	63	NR	Mean edu, years: 6.1	Dementia: NR MCI: NR	Medical history, physical and neurologic examinations, neuropsychological testing, and dementia-related blood tests

Table 2. Study and Population Characteristics of Included Diagnostic Accuracy Studies (KQ 2)

Author, year Quality	Country; recruitment setting	N Screened	Dem, %	MCI, %	Age, mean (range)	Female, %	Race/ Ethnicity, %	SES	Diagnostic Criteria	Reference Standard
Lipton, 2003[161] Fair	US; Community-based, Primary care	300	9	10	79 (≥65)	66	White: 83 Black: 15 Hispanic: 2	Mean edu, years: 12.8	Dementia: DSM-III-R MCI: NR	Clinical assessment and a case conference
Manly, 2011[162] Fair	US; Insurance list	377	14	18	81 (≥65)	68	White: 30 Black: 35 Hispanic: 34 Other: 1	Mean edu, years: 10.4	Dementia: DSM III-R MCI: NR	Medical history and neurologic and physical examination
Mao, 2018[458] Good	TWN; Community-based	10340	9	NR	76 (NR)	52	NR	Elementary school or less: 77%	Dementia: NIA-AA MCI: NA	Medical history, lifestyle factors, MMSE, AD8, CDR, cognitive and functional status
Markwick, 2012[163] Good	GBR; Community-based	107	8	19	76 (NR)	54	NR	≤12 years edu: 23.4%	Dementia: NINCDS-ADRDA, NINCDS-AIREN, Hachinski, DSM-IV MCI: Petersen criteria	Neuropsychological test battery, informant interview, medical history and examination, imaging, blood tests
McDowell, 1997[164] Fair	CAN; Community-based	1600	23	30	80 (65-99)	59	NR	Mean edu, years: 8.6	Dementia: DSM-III-R MCI: NR	Medical and family history, 3MS, physician's mental status assessment, and physical and neurological examination
Morales, 1997[165] Fair	ESP; Community-based	160	13	NR	73 (61-96)	68	NR	% Low economic level: 74.4	Dementia: DSM-III-R MCI: NA	Neurological and neuropsychological assessment
Ozer, 2016[166†] Fair	GBR; Primary care	152	0	26	78 (≥75)	NR	NR	Mean edu, years: 11.5	Dementia: NA MCI: Petersen criteria	Neuropsychological test battery, ADL, adult reading test
Rait, 2000[167] Fair	GBR; Primary care	101	11	NR	69 (≥60)	52	Asian: 100	Mean edu, years: 9	Dementia: GMS MCI: NA	GMS-AGECAT
Rait, 2000[168] Fair	GBR; Primary care	96	11	NR	69 (60-85)	50	Black: 100	Mean edu, years: 9	Dementia: GMS MCI: NA	GMS-AGECAT

Table 2. Study and Population Characteristics of Included Diagnostic Accuracy Studies (KQ 2)

Author, year Quality	Country; recruitment setting	N Screened	Dem, %	MCI, %	Age, mean (range)	Female, %	Race/ Ethnicity, %	SES	Diagnostic Criteria	Reference Standard
Ranson, 2018[459] Good	US; Community-based	824	35	NR	82 (70-110)	58	White: 72.2 Black: 18.0 Hispanic: 9.8	Mean edu, years: 10.1	Dementia: DSM-III-R and DSM-IV MCI: NA	Neuropsychological test battery, clinical examination, depression screen, and informant interview
Resichies, 1997[169] Fair	DEU; Community-based	516	20	NR	NR (≥70)	NR	NR	NR	Dementia: NR MCI: NA	GMS-A interview and History and Aetiology Schedule interview
Rideaux, 2012[170] Fair	US; Community-based	701	26	32	80 (≥70)	55	White: 72 Black: 18 Hispanic: 10	Mean edu, years: 10.3	Dementia: DSM-IV MCI: NR	Medical examination and neuropsychological test battery
Saxton, 2009[171] Good	US; Community-based, Primary care	524	0	44	73 (≥60)	65	White: 94	Mean edu, years: 13.5	Dementia: University of Pittsburgh ADRC MCI: University of Pittsburgh ADRC	Neuropsychological test battery, medical history, depression scale, IADL, subjective memory complaints
Solomon, 2000[172] Fair	US; Primary care	137	10	NR	77 (61-88)	67	NR	Mean edu, years: 11.8	Dementia: NINCDS-ADRDA MCI: NA	Medical history, history of cognitive complaints, physical examination, and neuropsychological testing
Stein, 2015[173†] Good	DEU; Primary care	2657	3	NR	81 (≥75)	65	NR	% Level of edu: Low=61 Middle=27 High=12	Dementia: DSM-IV MCI: NA	SIDAM
Swearer, 2002[174] Fair	US; Community-based, Primary care	46	17	NR	81 (NR)	65	NR	Mean edu, years: 14.4	Dementia: DSM-IV MCI: NA	Neuropsychological testing
Tariq, 2006[175] Fair	US; Primary care	702	12	26	75 (NR)	NR	NR	% HS edu or more: 69.4	Dementia: DSM-IV MCI: DSM-IV	Physical examination, laboratory testing, and mental status examination
Tokuhara, 2006[176] Fair	US; Primary care	230	7	10	74 (65-96)	66	Asian: 100	Mean edu, years: 12.2	Dementia: Benson and Cummings	Interview data, cognitive testing, and assessment of function

Table 2. Study and Population Characteristics of Included Diagnostic Accuracy Studies (KQ 2)

Author, year Quality	Country; recruitment setting	N Screened	Dem, %	MCI, %	Age, mean (range)	Female, %	Race/ Ethnicity, %	SES	Diagnostic Criteria	Reference Standard
									MCI: CASI<74 and CDR>0	
Vannier-Nitenberg, 2016[177]† Fair	FRA; Primary care	585	1	30	71 (≥65)	47	NR	No schooling/ primary edu: 32% Social deprivation (EPICES score): ≥30: 22% ≤30: 77%	Dementia: NINCDS-ARDA MCI: NINCDS-ARDA (amnestic MCI)	Neuropsychological test battery
Vercambre, 2010[178] Fair	FRA; Community-based	120	8	15	79 (NR)	100	NR	NR	Dementia: NR MCI: NR	Neuropsychological test battery
Waite, 1998[179] Fair	AUS; Community-based	630	28	NR	84 (78-99)	55	NR	Mean edu, years: 10	Dementia: DSM-IV criteria A and B MCI: NA	Medical history, neuropsychological test battery, and detailed medical and neurological examination
Wolf-Klein, 1989[180] Good	US; Other medical	312	47	NR	77 (58-99)	70	NR	NR	Dementia: NINCDS-ADRDA MCI: NA	History taking and physical examination

* Required memory problems if aged 50-74 years
† New study
‡ Recruited patients with memory concerns

Abbreviations: 3MS = Modified Mini-Mental State Examination; ADL = activities of daily living; ADRC = Aging and Disability Resource Center; AI/AN = American Indian/Alaskan Native; AUS = Australia; CAN = Canada; CASI = Cognitive Abilities Screening Instrument; CDR = Clinical Dementia Rating; Dem = dementia; DEU = Germany; DSM = Diagnostic and Statistical Manual of Mental Disorders; Edu = education; EPICES = Evaluation of Deprivation and Inequalities in Health Examination Centers; ESP = Spain; FIN = Finland; FRA = France; GBR = Great Britain/United Kingdom; GDS = Global Deterioration Scale; GMS-AGECAT = Geriatric Mental State – Automated Geriatric Examination for Computer Assisted Taxonomy; HKG = Hong Kong; IADL = instrumental activities of daily living; ICD-9 = International Statistical Classification of Diseases and Related Health Problems-9th revision; ICD-10 = International Statistical Classification of Diseases and Related Health Problems-10th revision; IRL = Ireland; KOR = Korea; MCI = mild cognitive impairment; N = number of participants; NA = not applicable; NINCDS/ADRDA = National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; NINDS-AIREN = National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences; NLD = Netherlands; NR = not reported; SD = standard deviation; SES = socioeconomic status; SGP = Singapore; SIDAM = Structured Interview for the Diagnosis of Dementias of the Alzheimer type and Multi-infarct dementia and dementias of other etiology; SWE = Sweden; TWN = Taiwan

Table 3. Screening Test Characteristics, by Category of Test (KQ 2)

Category	Test name (Target)*	Description	Domains
Very brief (5 minutes or less)	3-Word	3-item recall	Memory
	6-Item Screener	3-item recall plus 3 orientation questions	Memory
	AD8 (informant)	Asks informant about judgment, less interest in hobbies, repeats things, trouble using tools, forgets month or year, finances, trouble remembering appointments or daily things	Memory, Executive Functioning, Apraxia, Agnosia
	Clock Drawing Test, CDT	Clock draw; variety of scoring methods	Executive Functioning, Apraxia
	Cognitive Disorders Examination test, CoDEx	3-word test, simplified clock test and 5 spatial orientation questions from the MMSE	Memory, Executive Functioning, Apraxia
	Dubois five-word test	Recall of 5 word list	Memory
	Functional Activities Questionnaire, FAQ (informant)	Activities and independent activities of daily living, ability to remember appointments, ability to keep track of current events, understanding books	Memory, Executive Functioning, Apraxia
	General Practitioner Assessment of Cognition, GPCOG (patient and informant)	Recall, orientation, recent news recall. Patient questionnaire is paired with an informant questionnaire that asks about memory, finances, wordfinding, ADLs	Memory, Executive Functioning, Aphasia
	Hopkins Verbal Learning Test, HVLT	Immediate recall of objects	Memory
	Katz Activities of Daily Living, Katz ADL	Activities of daily living	Executive Functioning, Apraxia, Agnosia
	Lawton Instrumental Activities of Daily Living, Lawton IADL	Independent activities of daily living	Executive Functioning, Apraxia, Agnosia
	2-item functional memory screen, MF-2 (patient and informant)	Subjective memory complaints and trouble with executive function Note: This test can be completed by the informant or the patient	Memory, Executive Functioning
	Mini-Cog	3-item recall plus clock draw	Memory, Executive Functioning, Apraxia
	Memory Impairment Screen, MIS	4-item recall, either spontaneous or cued recall	Memory
	Memory Impairment Screen by Telephone, MIS-T	4-item recall, either spontaneous or cued recall administered by telephone	Memory
	Mental State Questionnaire, MSQ	Memory, orientation, naming, attention	Memory
	Orientation Memory Concentration, OMC	Memory, orientation, concentration	Memory
	Single-item (informant)	Asks about patient memory	Memory
	Short Portable Mental Status Questionnaire, SPMSQ	Orientation, memory, attention	Memory
	Short Test of Mental Status, STMS	Orientation, memory, attention	Memory
	Self-report memory impairment	Yes/No question: Do you feel like your memory is getting worse?	Memory

Table 3. Screening Test Characteristics, by Category of Test (KQ 2)

Category	Test name (Target)*	Description	Domains
	Sweet 16	Orientation (identification of person, place, time, and situation), registration, digit spans (tests of verbal memory), and recall	Memory
	Trail Making Tests, TMT	Different versions have patients go to different numbers/letters	Executive Functioning
	Visual Association Test, VAT	Visual association and recall	Memory, Apraxia
	Verbal Fluency, VF	Asks participant's name, and asks them to list as many different animals, first names, or similar objects as possible in 1 min	Memory, Aphasia, Executive Function
Brief (6-10 minutes)	7-Minute Screen, 7MS	Recall objects from categories, clock, vegetables	Memory, Executive Functioning, Aphasia, Apraxia, Agnosia
	Abbreviated Mental Test, AMT	Orientation, memory, name objects, attention tests	Memory, Agnosia
	Free and Cued Recall, FCR	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	Memory
	Abbreviated Fuld Object Memory Evaluation, FOME-abbreviated	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	Memory
	Immediate Recall	Evaluator reads a story, then asks patient to remember as many things from story as possible	Memory
	Kendrick Cognitive Tests	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	Memory
	Labyrinth Test - mistakes	Patient is asked to draw a line that successfully navigates through a maze	Apraxia
	Labyrinth Test - seconds	Patient is asked to draw a line that successfully navigates through a maze	Apraxia
	Memory Alteration Test, M@T	Assesses five cognitive skills: encoding, orientation, semantic memory, free recall, and cued recall	Memory
	MMblind	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	Memory, Aphasia
	Mini-Mental State Examination, MMSE	Orientation, recall, naming, draw figure, repetition, attention, reading, writing	Memory, Aphasia, Apraxia, Agnosia
	Montreal Cognitive Assessment. MoCA	Trails B, copy figure, clock, naming, verbal fluency, 5-word recall, similarities, orientation, attention	Memory, Executive Functioning, Aphasia, Apraxia, Agnosia
	Benton’s Orientation Test, OT	Identify month, date, year, day of the week, and time of day	Memory
	Short Blessed Test, SBT	Temporal orientation, attention, and short-term memory test	Memory

Table 3. Screening Test Characteristics, by Category of Test (KQ 2)

Category	Test name (Target)*	Description	Domains
	Saint Louis University Mental Status Examination, SLUMS	Orientation, 5-item recall, math, animals, attention, clock, figures, story	Memory, Executive Functioning, Aphasia, Apraxia, Agnosia
	Storandt Battery	Word fluency and trailmaking	Executive Functioning, Aphasia
	Telephone Instrument for Cognitive Status, TICS	Orientation, repetition, naming, and calculations are some of the items covered	Memory, Executive Functioning
	Modified Telephone Instrument for Cognitive Status, TICS-M	Orientation, repetition, naming, and calculations are some of the items covered	Memory, Executive Functioning
	Test Your Memory, TYM	Orientation, ability to copy a sentence, semantic knowledge, calculation, verbal fluency, similarities, naming, visuospatial abilities, recall of copied sentence	Memory, Executive Functioning, Aphasia, Apraxia
	Word List Learning - immediate recall	Immediate recall and recognition tasks. Recognition task is composed of 8 targets and 8 distractors	Memory
	Word List Learning - immediate recognition hit	Immediate recall and recognition tasks. Recognition task is composed of 8 targets and 8 distractors	Memory
	Word List Recognition	Tests immediate and delayed memory, and learning ability of non-associated verbal material. Patients are asked to recall as many of ten words as possible, immediately after having read them. After 5-10 minutes, patients are again asked to recall as many of the ten words presented before as possible, without seeing them. Finally, patients are asked to recognize the ten words among a list of 20 words.	Memory
Longer, Self-administered	Computer Assessment of Mild Cognitive Impairment, CAMCI	Orientation, figure identification, picture recall, word recall, attention, "virtual environment" (follow directions while driving)	Memory, Executive Functioning, Apraxia
	Cognitive Assessment Screening Test, CAST	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	Memory, Executive Functioning, Aphasia, Apraxia, Agnosia
	Concord Informant Dementia Scale, CIDS (informant)	Asks informant about changes in patient memory, orientation, judgment and problem solving, community affairs, involvement in home and hobbies, personal care, and language	Memory, Executive Functioning, Aphasia, Agnosia
	Informant Questionnaire on Cognitive Decline in the Elderly, IQCODE (informant)	Asks informant about changes in cognitive function, physical function, patient personality and behavior	Memory, Executive Functioning, Apraxia, Agnosia
	Short Informant Questionnaire on Cognitive Decline in the Elderly, IQCODE-Short (informant)	Same as full IQCODE, except has 16 rather than 26 questions	Memory, Executive Functioning, Apraxia, Agnosia
	Short Concord Informant Dementia Scale, SCIDS (informant)	Questions for informant about perceived changes in memory and ability to find their way around	Memory, Executive Functioning, Agnosia

*If not patient

Table 4. Test Performance of Very Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened group	% (n/N) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
3-Word	Dementia	Kuslansky, 2002[157]	All	12 (28/240)	240	0	0.65 (NR)	0.85 (NR)	0.37 (NR)	NR	0.80 (NR)
6-Item Screener	Dementia	Callahan, 2002[129]	All	4 (15/344)	344	≥3	0.887 (NR)	0.880 (NR)	0.248 (NR)	0.994 (NR)	0.95 (NR)
	Cognitive Impairment	Callahan, 2002[129]	All	26 (91/344)	344	≥2	0.742 (NR)	0.802 (NR)	0.574 (NR)	0.896 (NR)	0.86 (NR)
AD8	Dementia	Chan, 2016*[130]	60 years or older	24 (113/478)	309	≥4	0.91 (NR)	0.91 (NR)	0.63 (NR)	0.98 (NR)	0.97 (0.95, 0.99)
			75 years or older	24 (113/478)	110	≥4	0.90 (NR)	0.88 (NR)	0.79 (NR)	0.94 (NR)	0.95 (0.91, 0.99)
			79 years or older	24 (113/478)	59	≥4	0.87 (NR)	0.82 (NR)	0.84 (NR)	0.85 (NR)	0.90 (0.81, 0.98)
		Mao, 2018	All	9 (917/10340)	8805	1.5	0.88 (NR)	0.84 (NR)	NR	NR	0.90 (0.89, 0.92)
			Edu Elem School	NR	NR	1.5	0.84 (NR)	0.87 (NR)	NR	NR	0.90 (0.88, 0.92)
			Edu illiterate	NR	NR	1.5	0.92 (NR)	0.74 (NR)	NR	NR	0.89 (0.88, 0.91)
			Edu Jr HS or higher	NR	NR	1.5	0.82 (NR)	0.92 (NR)	NR	NR	0.91 (0.88, 0.95)
			Men	NR	NR	1.5	0.87 (NR)	0.87 (NR)	NR	NR	0.91 (0.89, 0.93)
			Women	NR	NR	1.5	0.88 (NR)	0.82 (NR)	NR	NR	0.90 (0.88, 0.91)
	MCI	Galvin, 2005[144]	All	29 (68/236)	180	≥2	NR	NR	NR	NR	0.834 (NR)
	Cognitive Impairment		All	53 (124/236)	236	≥2	0.85 (NR)	0.86 (NR)	0.76 (NR)	0.84 (NR)	0.904 (NR)
CDT	Dementia	Ball, 2001[125]	All	9 (10/170) (estimated)	53	NR	0.67 (NR)	0.69 (NR)	0.39 (NR)	0.91 (NR)	NR
		Del Ser, 2006[135]	All	12 (48/416)	416	NR (Freedman)	0.979 (NR)	0.807 (NR)	0.398 (NR)	0.996 (NR)	0.927 (NR)
		Fuchs, 2012[142]	All	5 (21/423)	423	≤7 (Sunderland)	0.895 (0.757, 1.00)	0.837 (0.801, 0.873)	0.207 (0.120, 0.295)	0.994 (0.986, 1.00)	0.856 (0.733, 0.978)
		Kirby, 2001[156]	All	6 (41/648)	648	≤5 (Sunderland)	NR	NR	NR	NR	NR (NR)
		Wolf-Klein, 1989[180]	All	47 (147/312)	312	Abnormal patterns	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
	MCI	Donnelly, 2008[136]	All	20 (20/100)	100	1 SD (Freedman)	0.85 (0.62, 0.97)	0.44 (0.33, 0.55)	0.27 (0.17, 0.40)	0.92 (0.79, 0.98)	0.73 (NR)

Table 4. Test Performance of Very Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened group	% (n/N) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
		Ehreke, 2009[138]	All-MCI modified	14 (58/428)	3198	≤9 (Sunderland)	0.594 (NR)	0.597 (NR)	NR	NR	0.616 (NR)
			All-MCI original	14 (58/428)	3198	≤9 (Sunderland)	0.582 (NR)	0.573 (NR)	NR	NR	0.595 (NR)
		Ehreke, 2009[138]	All	14 (58/428)	428	≤9 (Sunderland)	0.69 (NR)	0.63 (NR)	NR	NR	NR
			All	14 (58/428)	428	≥2 (Shulman)	0.76 (NR)	0.58 (NR)	NR (NR)	NR (NR)	NR
		Lee, 2008[160]	All	48 (224/465)	465	1/2 (CERAD)	0.430 (NR)	0.853 (NR)	0.245 (NR)	0.784 (NR)	0.656 (0.606, 0.706)
			All	48 (224/465)	465	9/10 (Freedman)	0.407 (NR)	0.830 (NR)	0.210 (NR)	0.748 (NR)	0.653 (0.604, 0.701)
			All	48 (224/465)	465	6/6.5 (Todd)	0.444 (NR)	0.813 (NR)	0.209 (NR)	0.716 (NR)	0.661 (0.613, 0.710)
			All	48 (224/465)	465	7/8 (Rouleau)	0.564 (NR)	0.718 (NR)	0.182 (NR)	0.559 (NR)	0.669 (0.621, 0.717)
CoDEx	Cognitive Impairment	Vannier-Nitenberg, 2016*[177]	All	31 (182/585)	491	NA	0.320 (NR)	0.848 (NR)	0.480 (NR)	0.739 (NR)	NR (NR)
Dubois five-word test	Cognitive Impairment		All	31 (182/585)	554	≤9	0.283 (NR)	0.892 (NR)	0.544 (NR)	0.733 (NR)	NR (NR)
FAQ	Dementia	Cruz-Orduna, 2011[132]	All	9 (15/160)	160	≥9	0.8667 (NR)	0.8207 (NR)	0.3333 (NR)	0.9835 (NR)	0.91 (0.84, 0.96)
	Dementia	Juva, 1997[152]	All	14 (93/656)	370	≥8	0.94 (NR)	0.84 (NR)	0.50 (NR)	NR (NR)	0.96 (0.92, 0.98)
	Cognitive Impairment	Cruz-Orduna, 2011[132]	All	56 (90/160)	160	≥2	0.7333 (NR)	0.7286 (NR)	0.7765 (NR)	0.68000 (NR)	0.77 (0.69, 0.84)
GPCOG	Dementia	Brodaty, 2002[127]	All	29 (82/283)	202	≤10	0.82 (NR)	0.83 (NR)	0.67 (NR)	0.92 (NR)	0.91 (0.86, 0.95)
HVLT	MCI	Donnelly, 2008[136]	All	20 (20/100)	100	1 SD	0.55 (0.32, 0.77)	0.43 (0.32, 0.54)	0.19 (0.10, 0.32)	0.79 (0.64, 0.90)	0.55 (NR)
Informant memory report	Dementia	Ayalon, 2011[124]	All	32 (206/647)	647	>2	NR	NR	NR	NR	NR
	MCI		All	29 (185/647)	441	>2	0.811 (NR)	0.753 (NR)	0.246 (NR)	0.188 (NR)	0.85 (NR)
	Cognitive Impairment		All	60 (391/647)	647	>2	NR	NR	NR	NR	NR

Table 4. Test Performance of Very Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened group	% (n/N) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
Katz ADL	Dementia	Juva, 1997[152]	All	14 (93/656)	437	≥2	0.81 (NR)	0.83 (NR)	0.42 (NR)	NR (NR)	0.90 (0.80, 0.94)
Lawton IADL	Dementia	Juva, 1997[152]	All	14 (93/656)	424	≤4	0.91 (NR)	0.86 (NR)	0.49 (NR)	NR (NR)	0.95 (0.91, 0.98)
		Mao, 2018[458]	All	9 (917/10340)	8805	6.5	0.89 (NR)	0.81 (NR)	NR	NR	0.925 (0.915, 0.935)
			Edu Elem School	NR	NR	6.5	0.87 (NR)	0.82 (NR)	NR	NR	0.916 (0.898, 0.934)
			Edu illiterate	NR	NR	6.5	0.89 (NR)	0.75 (NR)	NR	NR	0.913 (0.898, 0.929)
			Edu Jr HS or higher	NR	NR	6.5	0.94 (NR)	0.88 (NR)	NR	NR	0.947 (0.917, 0.978)
			Men	NR	NR	6.5	0.93 (NR)	0.78 (NR)	NR	NR	0.926 (0.910, 0.942)
			Women	NR	NR	6.5	0.86 (NR)	0.84 (NR)	NR	NR	0.928 (0.915, 0.940)
M@T - Cued recall	MCI	Ozer, 2016*[166]	All	26 (40/152)	152	<9	0.80 (NR)	0.78 (NR)	0.29 (NR)	0.97 (NR)	0.86 (0.78, 0.93)
M@T - Encoding	MCI		All	26 (40/152)	152	<9	0.58 (NR)	0.88 (NR)	0.35 (NR)	0.95 (NR)	0.79 (0.70, 0.87)
M@T - Free recall	MCI		All	26 (40/152)	152	<6	0.90 (NR)	0.77 (NR)	0.30 (NR)	0.99 (NR)	0.88 (0.82, 0.94)
M@T - Orientation	MCI		All	26 (40/152)	152	<5	0.38 (NR)	0.83 (NR)	0.20 (NR)	0.92 (NR)	0.61 (0.50, 0.71)
M@T - Semantic	MCI		All	26 (40/152)	152	<14	0.85 (NR)	0.54 (NR)	0.17 (NR)	0.97 (NR)	0.74 (0.65, 0.83)
MF-2	Dementia	Holsinger, 2012[147]	All	3 (21/630)	630	Both yes	0.38 (0.20, 0.60)	0.87 (0.84, 0.89)	NR (NR)	NR (NR)	NR (NR)
	Cognitive Impairment		All	42 (268/630)	630	Both yes	0.24 (0.19, 0.29)	0.93 (0.90, 0.95)	NR (NR)	NR (NR)	NR (NR)
Mini-Cog	Dementia	Borson, 2006[126]	All	42 (154/371)	371	≤2	NR	NR	NR	NR	NR

Table 4. Test Performance of Very Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened group	% (n/N) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
		Fuchs, 2012[142]	All	5 (21/423)	423	≤1	1.00 (0.824, 1.00)	0.852 (0.841, 0.884)	0.234 (0.153, 0.340)	1.00 (0.989, 1.00)	0.956 (0.931, 0.982)
		Holsinger, 2012[147]	All	3 (21/630)	630	≤2	0.76 (0.54, 0.90)	0.73 (0.69, 0.76)	NR (NR)	NR (NR)	NR (NR)
		Kaufer, 2008[154]	All	38 (55/146)	146	0	0.87 (0.76, 0.95)	0.54 (0.43, 0.64)	0.53 (NR)	0.88 (NR)	0.706 (NR)
	MCI		All	52 (76/146)	91	0	0.50 (0.38, 0.62)	0.73 (0.45, 0.92)	0.90 (NR)	0.22 (NR)	0.617 (NR)
	Cognitive Impairment	Borson, 2006[126]	All	62 (231/371)	371	≤2	NR	NR	NR	NR	NR
		Holsinger, 2012[147]	All	42 (268/630)	630	≤2	0.39 (0.34, 0.45)	0.78 (0.73, 0.82)	NR (NR)	NR (NR)	NR (NR)
		Kaufer, 2008[154]	All	90 (131/146)	146	0	NR	NR	NR	NR	NR
MIS	Dementia	Buschke, 1999	All	10 (50/483)	483	4	0.80 (NR)	0.96 (NR)	0.69 (NR)	0.98 (NR)	0.94 (NR)
		Holsinger, 2012[147]	All	3 (21/630)	630	≤4	0.43 (0.24, 0.64)	0.93 (0.90, 0.95)	NR (NR)	NR (NR)	NR (NR)
		Kuslansky, 2002[157]	All	12 (28/240)	240	≤4	0.86 (NR)	0.97 (NR)	0.80 (NR)	NR	0.93 (NR)
		Ranson, 2018[459]	All	35 (291/824)	824	≤4	0.82 (0.77, 0.86)	0.85 (0.82, 0.88)	0.48 (0.42, 0.53)	0.97 (0.96, 0.97)	NR
	Cognitive Impairment	Holsinger, 2012[147]	All	42 (268/630)	630	≤4	0.17 (0.13, 0.22)	0.98 (0.96, 0.99)	NR (NR)	NR (NR)	NR (NR)
MIS-T	Dementia	Lipton, 2003[161]	All-extrapolated	9 (27/300)	300	4	0.78 (NR)	0.93 (NR)	0.52 (NR)	NR (NR)	0.92 (NR)
MSQ	Dementia	Fillenbaum, 1990[140]	All	16 (26/159)	159	≤7	NR	NR	NR	NR	NR
		Hooijer, 1992[148]	All	3.6 (13/358)	358	≤7	0.923 (NR)	0.983 (NR)	0.667 (NR)	NR (NR)	NR (NR)
OMC	Dementia	Fillenbaum, 1990[140]	All	16 (26/159)	159	≥11	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR
Self-report	Dementia	Fuchs, 2012[142]	All	5 (21/423)	423	NA	0.895 (0.757, 1.00)	0.458 (0.409, 0.506)	0.073 (0.039, 0.506)	0.989 (0.974, 1.00)	NR
SPMSQ	Dementia	Del Ser, 2006[135]	All	12 (48/416)	416	NR	0.958 (NR)	0.885 (NR)	0.522 (NR)	0.993 (NR)	0.978 (NR)
	Dementia	Erkinjuntti, 1987[139]	All	2 (3/119)	119	≤7	1.00 (NR)	1.00 (NR)	1.00 (NR)	1.00 (NR)	NR

Table 4. Test Performance of Very Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened group	% (n/N) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
	Dementia	Fillenbaum, 1990[140]	All	16 (26/159)	159	NR	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR
	Dementia	Hooijer, 1992[148]	All	3.6 (13/358)	358	≤7	1.0 (NR)	0.968 (NR)	0.542 (NR)	NR (NR)	NR (NR)
STMS	MCI	Cummings-Vaughn, 2014*[134]	All	42 (57/136)	108	≤32	0.68 (NR)	0.76 (NR)	0.76 (NR)	0.68 (NR)	0.77 (0.68, 0.86)
	Cognitive Impairment		All	62 (85/136)	136	≤32	0.78 (NR)	0.76 (NR)	0.85 (NR)	0.67 (NR)	0.84 (0.77, 0.90)
Sweet 16	Dementia	Fong, 2011[141]	All	1 (86/709)	729	<14	0.99 (0.97, 1.00)	0.72 (0.68, 0.77)	0.33 (0.28, 0.39)	1.00 (0.99, 1.00)	0.97 (NR)
TMT	Dementia	Heun, 1998[146]	All	13 (37/287)	287	≤40	0.81 (NR)	0.71 (NR)	NR (NR)	NR (NR)	0.836 (0.756, 0.916)
TMT A	MCI	Donnelly, 2008[136]	All	20 (20/100)	100	1 SD	0.30 (0.12, 0.54)	0.90 (0.81, 0.96)	0.43 (0.18, 0.71)	0.84 (0.74, 0.91)	0.72 (NR)
TMT B	MCI		All	20 (20/100)	100	1 SD	0.43 (0.18, 0.71)	0.86 (0.76, 0.93)	0.35 (0.14, 0.62)	0.89 (0.80, 0.95)	0.66 (NR)
TYM - Calculation	MCI	Ozer, 2016*[166]	All	26 (40/152)	152	<4	0.40 (NR)	0.73 (NR)	0.14 (NR)	0.92 (NR)	0.58 (0.47, 0.69)
TYM - Copying	MCI	Ozer, 2016*[166]	All	26 (40/152)	152	<1	0.05 (NR)	0.99 (NR)	0.85 (NR)	0.95 (NR)	0.52 (0.49, 0.67)
TYM - Fluency	MCI		All	26 (40/152)	152	<4	0.73 (NR)	0.66 (NR)	0.19 (NR)	0.96 (NR)	0.72 (0.63, 0.82)
TYM - Free recall	MCI		All	26 (40/152)	152	<3	0.50 (NR)	0.93 (NR)	0.44 (NR)	0.94 (NR)	0.72 (0.62, 0.82)
TYM - Help	MCI		All	26 (40/152)	152	<4	0.13 (NR)	0.93 (NR)	0.17 (NR)	0.91 (NR)	0.53 (0.43, 0.64)
TYM - Naming	MCI		All	26 (40/152)	152	<5	0.13 (NR)	0.96 (NR)	0.27 (NR)	0.91 (NR)	0.54 (0.43, 0.65)
TYM - Orientation	MCI		All	26 (40/152)	152	<10	0.30 (NR)	0.83 (NR)	0.16 (NR)	0.91 (NR)	0.57 (0.46, 0.67)
TYM - Semantic	MCI		All	26 (40/152)	152	<2	0.40 (NR)	0.91 (NR)	0.33 (NR)	0.93 (NR)	0.67 (0.56, 0.77)
TYM - Similarities	MCI		All	26 (40/152)	152	<4	0.53 (NR)	0.68 (NR)	0.16 (NR)	0.93 (NR)	0.61 (0.51, 0.72)
TYM - Visuospatial 1	MCI		All	26 (40/152)	152	<1	0.13 (NR)	0.94 (NR)	0.19 (NR)	0.91 (NR)	0.50 (0.40, 0.61)

Table 4. Test Performance of Very Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened group	% (n/N) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
TYM - Visuospatial 2	MCI		All	26 (40/152)	152	<4	0.15 (NR)	0.90 (NR)	0.14 (NR)	0.91 (NR)	0.53 (0.42, 0.63)
VAT	Dementia	Fuchs, 2012[142]	All	5 (21/423)	423	7/8	0.952 (0.861, 1.00)	0.960 (0.941, 0.979)	0.556 (0.393, 0.718)	0.997 (0.992, 1.00)	0.981 (0.963, 0.999)
VFT	Dementia	Del Ser, 2006[135]	All	12 (48/416)	416	NR	0.979 (NR)	0.839 (NR)	0.443 (NR)	0.996 (NR)	0.975 (NR)
VFT	Dementia	Fuchs, 2012[142]	All	5 (21/423)	423	≤12	0.895 (0.757, 1.00)	0.883 (0.851, 0.914)	0.266 (0.157, 0.374)	0.994 (0.987, 1.00)	0.918 (0.833, 1.002)
VFT	Dementia	Lipton, 2003[161]	All-extrapolated	9 (27/300)	300	19	0.68 (NR)	0.88 (NR)	0.36 (NR)	NR (NR)	0.89 (NR)
VFT	Cognitive Impairment	Vannier-Nitenberg, 2016*[177]	All	31 (182/585)	553	NA	0.247 (NR)	0.885 (NR)	0.506 (NR)	0.712 (NR)	NR (NR)
VFT - animals	Dementia	Ranson, 2018[459]	All	35 (291/824)	824	≤8	0.78 (0.73, 0.83)	0.90 (0.87, 0.92)	0.55 (0.48, 0.61)	0.96 (0.95, 0.91)	0.92 (NR)
VFT - animals and names	Dementia	Heun, 1998[146]	All	13 (37/287)	287	≤30	0.84 (NR)	0.81 (NR)	NR	NR	0.902 (0.806, 0.998)
VFT - animals category	Dementia	Heun, 1998[146]	All	13 (37/287)	287	≤14	0.81 (NR)	0.83 (NR)	NR (NR)	NR (NR)	0.886 (0.828, 0.942)
VFT - repeated animal names	Dementia	Heun, 1998[146]	All	13 (37/287)	287	≤1	0.31 (NR)	0.76 (NR)	NR	NR	0.533 (0.423, 0.643)
VFT - repeated first names	Dementia	Heun, 1998[146]	All	13 (37/287)	287	≤1	0.32 (NR)	0.70 (NR)	NR	NR	0.512 (0.402, 0.622)

* New study

Abbreviations: 3-Word = 3-Word Memory Test; AD8 = 8-item informant interview; ADL = activities of daily living; AUC = area under the curve; CDT = Clock Drawing Test; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CI = confidence interval; CoDEx = Cognitive Disorders Examination test; FAQ = Functional Activities Questionnaire; GPCOG = General Practitioner Assessment of Cognition; HVLT = Hopkins Verbal Learning Test; IADL = instrumental activities of daily living; KQ = key question; M@T = Memory Alteration Test; MCI = mild cognitive impairment; MCI = mild cognitive impairment; MF-2 = 2-item functional memory screen; MIS/MIS-T = Memory Impairment Screen/Memory Impairment Screen by Telephone; MSQ/SPMSQ = Mental Health Status Questionnaire/Short Portable Mental Status Questionnaire; N = number of participants; NA = not applicable; NPV = negative predictive value; NR = not reported; OMC = Orientation Memory Concentration; PPV = positive predictive value;

Table 4. Test Performance of Very Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

SD = standard deviation; STMS = Short Test of Mental Status; TMT = Trail Making Test; TYM = Test Your Memory; Sens = sensitivity; Spec = specificity; VAT = Visual Association Test; VFT = Verbal Fluency Test

Table 5. Test Performance of Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened Group	Percent (n/n) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
7MS	Dementia	Del Ser, 2006[135]	All	12 (48/416)	416	NR	1.00 (NR)	0.951 (NR)	0.786 (NR)	1.00 (NR)	0.996 (NR)
		Solomon, 2000[172]	All	10 (13/137)	137	≥0.7	NR	NR	NR	NR	NR
AMT	Dementia	Brodaty, 2002[127]	All	29 (82/283)	269	≤7	0.42 (NR)	0.93 (NR)	0.71 (NR)	0.80 (NR)	0.78 (0.71, 0.84)
		Hooijer, 1992[148]	All	3.6 (13/358)	358	≤7	0.923 (NR)	0.954 (NR)	0.429 (NR)	NR	NR
		Rait, 2000[168]	All	6 (6/96)	96	≤7	1.0 (0.54, 1.0)	0.83 (0.76, 0.91)	NR	NR	NR
		Rait, 2000[167]	Gujarati	11 (13/120)	62	≤5	1.0 (0.16, 1.0)	0.95 (0.858, 0.99)	NR	NR	NR
			Pakistani	NR	39	≤6	1.0 (0.664, 1.0)	0.867 (0.684, 0.956)	NR	NR	NR
FCR	Dementia	Del Ser, 2006[135]	All	12 (48/416)	416	NR	1.00 (NR)	0.872 (NR)	0.505 (NR)	1.00 (NR)	0.994 (NR)
FOME-abbreviated	Cognitive Impairment	Rideaux, 2012[170]	Black	57 (401/701)	87	≤21	0.65 (0.55, 0.75)	0.74 (0.64, 0.83)	0.76 (0.67, 0.85)	0.62 (0.52, 0.72)	NR
			Latino	57 (401/701)	55	≤24	0.93 (NR)	0.57 (NR)	NR	NR	NR
			White	57 (401/701)	380	≤20	0.55 (0.50, 0.60)	0.93 (0.91, 0.96)	0.83 (0.80, 0.87)	0.80 (0.75, 0.84)	NR
Immediate Recall	Dementia	Fuchs, 2012[142]	All	5 (21/423)	423	≤14	1.00 (1.00, 1.00)	0.828 (0.790, 0.865)	0.207 (0.122, 0.292)	1.00 (1.00, 1.00)	0.957 (0.927, 0.987)
Kendrick Cognitive Tests	Dementia	Fillenbaum, 1990	All	16 (26/159)	159	NA	NR	NR	NR	NR	NR
Labyrinth Test - mistakes	Dementia	Heun, 1998[146]	All	13 (37/287)	287	≤3	0.88 (NR)	0.60 (NR)	NR	NR	0.802 (0.716, 0.888)
Labyrinth Test - seconds	Dementia	Heun, 1998[146]	All	13 (37/287)	287	≤80	0.56 (NR)	0.84 (NR)	NR	NR	0.725 (0.592, 0.858)
M@T	MCI	Ozer, 2016*[166]	All	26 (40/152)	152	<40	0.85 (NR)	0.84 (NR)	0.37 (NR)	0.98 (NR)	0.91 (0.85, 0.96)
MMblind	Dementia	Resichies, 1997[169]	70-84 years	20 (100/491)	248	18/19	0.812 (NR)	0.894 (NR)	NR	NR	NR
			85-95+ years	20 (100/491)	243	16/17	0.734 (NR)	0.781 (NR)	NR	NR	NR
			All	20 (100/491)	491	17/18	0.849 (NR)	0.821 (NR)	NR	NR	NR

Table 5. Test Performance of Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened Group	Percent (n/n) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
MMSE	Dementia	Brodaty, 2002[127]	All	29 (82/283)	283	≤24	0.81 (NR)	0.76 (NR)	0.57 (NR)	0.90 (NR)	0.85 (0.80, 0.90)
		Callahan, 2002[129]	All	4 (15/344)	344	≤24	0.984 (NR)	0.836 (NR)	0.248 (NR)	0.994 (NR)	0.96 (NR)
			All	4 (15/344)	344	≤23	0.952 (NR)	0.867 (NR)	0.242 (NR)	0.998 (NR)	0.96 (NR)
		Chan, 2016*[130]	60 years or older	24 (113/478)	309	≤20	0.75 (NR)	0.94 (NR)	0.66 (NR)	0.96 (NR)	0.92 (0.88, 0.97)
			75 years or older	24 (113/478)	110	≤17	0.71 (NR)	0.92 (NR)	0.82 (NR)	0.86 (NR)	0.87 (0.79, 0.94)
			79 years or older	24 (113/478)	59	≤19	0.81 (NR)	0.86 (NR)	0.86 (NR)	0.80 (NR)	0.84 (0.74, 0.95)
		Cruz-Orduna, 2011[132]	All	9 (15/160)	160	≤18	0.8000 (NR)	0.8621 (NR)	0.5750 (NR)	0.9766 (NR)	0.89 (0.82, 0.95)
		Cullen, 2005[133]	All	4 (44/1115)	1115	≤23	0.909 (NR)	0.871 (NR)	NR	NR	NR
		Fillenbaum, 1990[140]	All	16 (26/159)	159	≤23	NR	NR	NR	NR	NR
		Fong, 2011[141]	All	1 (86/709)	709	≤23	0.87 (0.78, 0.95)	0.89 (0.86, 0.92)	0.52 (0.44, 0.60)	0.98 (0.99, 0.99)	0.95 (NR)
		Gagnon, 1990[143]	All	4 (10/2730)	2730	24	1.00 (NR)	0.78 (NR)	0.15 (NR)	NR	NR
		Grut, 1993[145]	All	14 (255/810)	1810	≤23	0.87 (NR)	0.92 (NR)	0.68 (NR)	NR	NR
		Heun, 1998[146]	All	13 (37/287)	287	≤23	0.84 (NR)	0.99 (NR)	NR	NR	0.988 (0.880, 1.0)
			All	13 (37/287)	287	≤24	0.92 (NR)	0.96 (NR)	NR	NR	0.988 (0.880, 1.0)
	Dementia	Hooijer, 1992[148]	All	3.6 (13/358)	358	≤23	0.769 (NR)	0.965 (NR)	0.455 (NR)	NR	NR
		Chan, 2016*[130]	13 years edu or more	6 (16/276)	97	27.5	0.63 (NR)	1.00 (NR)	NR	NR	NR
			6 years edu or less	6 (16/276)	61	24.5	0.79 (NR)	0.75 (NR)	NR	NR	0.7965 (0.60, 0.99)
			60-69 years	6 (16/276)	171	25.5	0.85 (NR)	1.00 (NR)	NR	NR	0.8925 (0.83, 0.96)
			70-79 years	6 (16/276)	91	24.5	0.87 (NR)	0.38 (NR)	NR	NR	0.6456 (0.44, 0.85)
			7-12 years edu	6 (16/276)	118	28.5	0.41 (NR)	0.88 (NR)	NR	NR	0.6290 (0.45, 0.81)
			80 years or more	6 (16/276)	14	28.5	0.27 (NR)	1.00 (NR)	NR	NR	0.5758 (0.19, 0.96)
			All	6 (16/276)	276	28.5	0.38 (NR)	0.92 (NR)	NR	NR	0.6976 (0.56, 0.83)

Table 5. Test Performance of Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened Group	Percent (n/n) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
			Men	6 (16/276)	136	28.5	0.35 (NR)	1.00 (NR)	NR	NR	0.6717 (0.51, 0.84)
			Women	6 (16/276)	140	25.5	0.77 (NR)	0.67 (NR)	NR	NR	0.7317 (0.50, 0.96)
		Jeong, 2004[150]	All	20 (46/235)	235	≤18	0.91 (0.79, 0.98)	0.76 (0.69, 0.82)	NR	NR	0.89 (NR)
		Jorm, 1996[151]	All	NR	NR	≤26	0.67 (NR)	0.85 (NR)	NR	NR	0.81 (NR)
		Kahle-Wrobleski, 2007[153]	Age 90 to 93 college grad	36 (155/435)	63	25	0.82 (NR)	0.80 (NR)	NR	NR	0.90 (NR)
			Age 90 to 93 some college	36 (155/435)	57	22	0.92 (NR)	0.96 (NR)	NR	NR	0.98 (NR)
			Age 90-93 HS edu or less	36 (155/435)	49	23	0.87 (NR)	0.94 (NR)	NR	NR	0.92 (NR)
			Age 94 to 96 college grad	36 (155/435)	74	24	0.85 (NR)	0.80 (NR)	NR	NR	0.92 (NR)
	Dementia	Kahle-Wrobleski, 2007[153]	Age 94 to 96 some college	36 (155/435)	43	25	0.88 (NR)	0.85 (NR)	NR	NR	0.94 (NR)
			Age 94-96 HS edu or less	36 (155/435)	35	23	0.90 (NR)	0.93 (NR)	NR	NR	0.94 (NR)
			Age 97 or over college grad	36 (155/435)	49	23	0.89 (NR)	0.90 (NR)	NR	NR	0.95 (NR)
			Age 97 or over HS edu or less	36 (155/435)	32	22	0.80 (NR)	0.76 (NR)	NR	NR	0.93 (NR)
			Age 97 or over some college	36 (155/435)	33	24	0.94 (NR)	0.88 (NR)	NR	NR	0.93 (NR)
		Kaufer, 2008[154]	All	38 (55/146)	146	≤26	0.82 (0.69, 0.91)	0.67 (0.56, 0.77)	0.60 (NR)	0.86 (NR)	0.854 (NR)
		Kay, 1985[155]	All	14 (39/274)	274	≤24	0.846 (NR)	0.808 (NR)	NR	NR	NR
		Kirby, 2001[156]	All	6 (41/648)	648	≤23	NR	NR	NR	NR	NR

Table 5. Test Performance of Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened Group	Percent (n/n) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
		Lam, 2008[158]	All	10 (44/459)	459	NR	NR	NR	NR	NR	0.811 (NR)
		McDowell, 1997[164]	All	23 (368/1600)	1600	24	0.63 (NR)	0.89 (NR)	NR	NR	0.89 (NR)
		Mao, 2018[458]	All	9 (917/10340)	8805	20.5	0.89 (,)	0.82 (,)	(,)	(,)	0.93 (0.92, 0.94)
			Edu Elem School	NR	NR	21.5	0.89 (,)	0.85 (,)	(,)	(,)	0.94 (0.92, 0.95)
			Edu illiterate	NR	NR	15.5	0.89 (,)	0.91 (,)	(,)	(,)	0.95 (0.94, 0.96)
			Edu Jr HS or higher	NR	NR	24.5	0.90 (,)	0.80 (,)	(,)	(,)	0.94 (0.92, 0.97)
			Men	NR	NR	21.5	0.87 (,)	0.85 (,)	(,)	(,)	0.93 (0.92, 0.94)
			Women	NR	NR	17.5	0.84 (,)	0.90 (,)	(,)	(,)	0.94 (0.25, 0.95)
		Morales, 1997[165]	Rural	13 (34/257)	160	20	0.83 (NR)	0.74 (NR)	0.34 (NR)	0.95 (NR)	NR
		Rait, 2000[168]	All	6 (6/96)	96	≤25	0.83 (0.76, 0.91)	0.78 (0.69, 0.86)	NR	NR	NR
	Dementia	Rait, 2000[167]	Gujarati	11 (13/120)	62	≤23	1.0 (0.16, 1.0)	0.95 (0.858, 0.99)	NR	NR	NR
			Pakistani	NR	39	≤26	1.0 (0.664, 1.0)	0.767 (0.573, 0.894)	NR	NR	NR
		Ranson, 2018[459]	All	35 (291/824	824	≤23	0.931 (0.896, 0.958)	0.713 (0.672, 0.751)	0.344 (0.313, 0.375)	0.985 (0.977, 0.990)	0.94 (NR)
		Resichies, 1997[169]	70-84 years	20 (100/491)	236	≤26	0.80 (NR)	0.824 (NR)	NR	NR	NR
			85-95+ years	20 (100/491)	213	≤23	0.851 (NR)	0.753 (NR)	NR	NR	NR
		Resichies, 1997[169]	All	20 (100/491)	449	≤24	0.841 (NR)	0.831 (NR)	NR	NR	NR
			All	20 (100/491)	449	≤23	0.78 (NR)	0.876 (NR)	NR	NR	NR
		Stein, 2015*[173]	All	3 (86/2657)	2657	≤24	0.930 (NR)	0.959 (NR)	0.432 (NR)	0.997 (NR)	0.979 (0.965, 0.993)
		Tariq, 2006[175]	HS edu or more	12 (82/702)	488	≤28.5	NR	NR	NR	NR	NR
			Less than HS edu	12 (82/702)	214	≤27.5	NR	NR	NR	NR	NR

Table 5. Test Performance of Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened Group	Percent (n/n) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
		Waite, 1998[179]	All	28 (99/360)	360	≤23	0.84 (NR)	0.88 (NR)	NR	NR	0.93 (NR)
	MCI	Donnelly, 2008[136]	All	20 (20/100)	100	1 SD	0.20 (0.06, 0.44)	0.93 (0.84, 0.97)	0.40 (0.12, 0.74)	0.82 (0.73, 0.89)	0.72 (NR)
	MCI	Kaufer, 2008[154]	All	52 (76/146)	91	≤27	0.47 (0.36, 0.59)	0.73 (0.45, 0.92)	0.90 (NR)	0.22 (NR)	0.666 (NR)
	MCI	Saxton, 2009[171]	All	44 (228/524)	524	28	0.45 (NR)	0.80 (NR)	NR	NR	NR
	MCI	Tariq, 2006[175]	HS edu or more	26 (180/702)	433	≤29.5	0.75 (NR)	0.48 (NR)	0.38 (NR)	0.82 (NR)	0.643 (NR)
	MCI		Less than HS edu	26 (180/702)	187	≤28.5	0.60 (NR)	0.65 (NR)	0.38 (NR)	0.82 (NR)	0.671 (NR)
	Cognitive Impairment	Callahan, 2002[129]	All	26 (91/344)	344	≤25	0.715 (NR)	0.873 (NR)	0.669 (NR)	0.895 (NR)	0.84 (NR)
	Cognitive Impairment	Cruz-Orduna, 2011[132]	All	56 (90/160)	160	≤23	0.7667 (NR)	0.7000 (NR)	0.7667 (NR)	0.7000 (NR)	0.82 (0.76, 0.88)
	Cognitive Impairment	Cullen, 2005[133]	All	9 (97/1115)	1115	≤23	0.722 (NR)	0.894 (NR)	NR	NR	NR
	Cognitive Impairment	Jeong, 2004[150]	All	42 (100/235)	235	≤20	0.82 (0.73, 0.89)	0.79 (0.71, 0.86)	NR	NR	0.89 (NR)
	Cognitive Impairment	Jorm, 1996[151]	All	NR	NR	NR	NR	NR	NR	NR	0.70 (NR)
	Cognitive Impairment	Kaufer, 2008[154]	All	90 (131/146)	146	≤26	NR	NR	NR	NR	NR
	Cognitive Impairment	Lam, 2008[158]	All	45 (206/459)	459	NR	NR	NR	NR	NR	0.961 (NR)
	Cognitive Impairment	McDowell, 1997[164]	All	53 (848/1600)	1600	NR	NR	NR	NR	NR	0.77 (NR)
	Cognitive Impairment	Rideaux, 2012[170]	Black	57 (401/701)	87	≤22	0.67 (NR)	0.71 (NR)	NR	NR	NR
	Cognitive Impairment		Latino	57 (401/701)	55	≤24	0.93 (0.86, 1.0)	0.71 (0.60, 0.83)	0.93 (0.64, 0.87)	0.71 (0.83, 0.99)	NR
	Cognitive Impairment		White	57 (401/701)	380	≤25	0.58 (NR)	0.86 (NR)	NR	NR	NR
	Cognitive Impairment	Tariq, 2006[175]	HS edu or more	37 (262/702)	488	≤28.5	NR	NR	NR	NR	NR
	Cognitive Impairment		Less than HS edu	37 (262/702)	214	≤27.5	NR	NR	NR	NR	NR
	Cognitive Impairment	Vercambre, 2010[178]	All	23 (28/120)	120	NR	NR	NR	NR	NR	0.72 (NR)

Table 5. Test Performance of Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened Group	Percent (n/n) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
MoCA	Dementia	Chan, 2016*[130]	60 years or older	24 (113/478)	309	≤16	0.84 (NR)	0.89 (NR)	0.56 (NR)	0.97 (NR)	0.94 (0.92, 0.97)
	Dementia		75 years or older	24 (113/478)	110	≤12	0.76 (NR)	0.88 (NR)	0.76 (NR)	0.88 (NR)	0.88 (0.82, 0.95)
	Dementia		79 years or older	24 (113/478)	59	≤12	0.81 (NR)	0.86 (NR)	0.86 (NR)	0.80 (NR)	0.87 (0.78, 0.96)
	Dementia	Hsu, 2015*[149]	13 years edu or more	6 (16/276)	97	22.5	0.92 (NR)	1.00 (NR)	NR	NR	NR
	Dementia	Hsu, 2015*[149]	6 years edu or less	6 (16/276)	61	20.5	0.89 (NR)	1.00 (NR)	NR	NR	0.9709 (0.91, 1.00)
	Dementia		60-69 years	6 (16/276)	171	23.5	0.84 (NR)	1.00 (NR)	NR	NR	0.9625 (0.90, 1.00)
	Dementia		70-79 years	6 (16/276)	91	23.5	0.67 (NR)	0.88 (NR)	NR	NR	0.8244 (0.71, 0.94)
	Dementia		7-12 years edu	6 (16/276)	118	23.5	0.80 (NR)	0.90 (NR)	NR	NR	0.8465 (0.75, 0.94)
	Dementia		80 years or more	6 (16/276)	14	22.0	0.73 (NR)	1.00 (NR)	NR	NR	0.8788 (0.69, 1.00)
	Dementia		All	6 (16/276)	276	23.5	0.78 (NR)	0.94 (NR)	NR	NR	0.8913 (0.83, 0.96)
	Dementia		Men	6 (16/276)	136	22.5	0.84 (NR)	0.88 (NR)	NR	NR	0.8882 (0.79, 0.98)
	Dementia		Women	6 (16/276)	140	23.5	0.76 (NR)	1.00 (NR)	NR	NR	0.8984 (0.81, 0.99)
	Dementia	Lee, 2008[159]	All	22 (44/196)	196	≤22	NR	NR	NR	NR	NR
	Dementia	Markwick, 2012[163]	All	8 (8/107)	107	<26	NR	NR	NR	NR	NR
	MCI	Cummings-Vaughn, 2014*[134]	All	42 (57/136)	108	≤24	0.72 (NR)	0.75 (NR)	0.76 (NR)	0.70 (NR)	0.77 (0.68, 0.86)
	MCI		All	42 (57/136)	108	≤25	0.81 (NR)	0.55 (NR)	0.67 (NR)	0.72 (NR)	0.77 (0.68, 0.86)
	MCI	Lee, 2008[159]	All	19 (37/196)	152	≤22	0.89 (NR)	0.84 (NR)	0.65 (NR)	0.96 (NR)	0.94 (0.90, 0.98)
	MCI	Markwick, 2012[163]	All	19 (20/107)	99	<26	NR	NR	NR	NR	NR
	Cognitive Impairment	Cummings-Vaughn, 2014*[134]	All	62 (85/136)	136	≤24	0.80 (NR)	0.75 (NR)	0.84 (NR)	0.69 (NR)	0.83 (0.77, 0.90)

Table 5. Test Performance of Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened Group	Percent (n/n) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
	Cognitive Impairment		All	62 (85/136)	136	≤25	0.86 (NR)	0.55 (NR)	0.76 (NR)	0.70 (NR)	0.83 (0.77, 0.90)
	Cognitive Impairment	Lee, 2008[159]	All	41 (81/196)	196	≤22	NR	NR	NR	NR	NR
	Cognitive Impairment	Markwick, 2012[163]	All	26 (28/107)	107	<26	NR	NR	NR	NR	NR
OT	Dementia	Del Ser, 2006[135]	All	12 (48/416)	416	NR	0.958 (NR)	0.855 (NR)	0.464 (NR)	0.993 (NR)	0.970 (NR)
SBT	Dementia	Ball, 2001[125]	All	9 (10/170) (estimated)	53	>8	0.40 (NR)	0.89 (NR)	0.67 (NR)	0.87 (NR)	NR
SLUMS	Dementia	Tariq, 2006[175]	HS edu or more	12 (82/702)	488	≤24.5	NR	NR	NR	NR	NR
	Dementia		Less than HS edu	12 (82/702)	214	≤22.5	NR	NR	NR	NR	NR
	MCI	Cummings-Vaughn, 2014*[134]	All	42 (57/136)	108	≤26	0.74 (NR)	0.65 (NR)	0.70 (NR)	0.69 (NR)	0.74 (065, 0.84)
	MCI	Tariq, 2006[175]	HS edu or more	26 (180/702)	433	≤25.5	0.95 (NR)	0.76 (NR)	0.74 (NR)	0.93 (NR)	0.643 (NR)
	MCI		Less than HS edu	26 (180/702)	187	≤23.5	0.92 (NR)	0.81 (NR)	0.64 (NR)	0.97 (NR)	0.927 (NR)
	Cognitive Impairment	Cummings-Vaughn, 2014*[134]	All	62 (85/136)	136	≤25	0.72 (NR)	0.75 (NR)	0.82 (NR)	0.61 (NR)	0.82 (0.75, 0.89)
	Cognitive Impairment	Tariq, 2006[175]	HS edu or more	37 (262/702)	488	≤24.5	NR	NR	NR	NR	NR
	Cognitive Impairment		Less than HS edu	37 (262/702)	214	≤22.5	NR	NR	NR	NR	NR
SMMSE	Dementia	Stein, 2015*[173]	All	3 (86/2657)	2657	≤4	0.976 (NR)	0.711 (NR)	0.101 (NR)	0.998 (NR)	0.909 (0.884, 0.935)
Storandt Battery	Dementia	Fillenbaum, 1990[140]	All	16 (26/159)	159	≥0	NR	NR	NR	NR	NR
TICS	Dementia	Lipton, 2003[161]	All	9 (27/300)	300	28	0.74 (NR)	0.93 (NR)	0.34 (NR)	NR	0.86 (NR)
	Dementia	Manly, 2011[162]	All	14 (53/377)	377	≤22	0.88 (NR)	0.87 (NR)	0.51 (NR)	0.98 (NR)	0.94 (NR)
	Cognitive Impairment		All	32 (121/377)	377	≤26	0.73 (NR)	0.77 (NR)	0.59 (NR)	0.86 (NR)	0.81 (NR)
	Cognitive Impairment	Vercambre, 2010[178]	All	23 (28/120)	120	NR	NR	NR	NR	NR	0.78 (NR)
TICS-M	MCI	Cook, 2009[131]	All	24 (17/71)	71	34	0.824 (NR)	0.870 (NR)	0.667 (NR)	0.940 (NR)	0.933 (NR)
TICS-M	Cognitive Impairment	Vercambre, 2010[178]	All	23 (28/120)	120	31	0.71 (NR)	0.83 (NR)	0.56 (NR)	0.90 (NR)	0.83 (NR)

Table 5. Test Performance of Brief Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened Group	Percent (n/n) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
TYM	MCI	Ozer, 2016*[166]	All	26 (40/152)	152	<43	0.63 (NR)	0.87 (NR)	0.35 (NR)	0.95 (NR)	0.80 (0.72, 0.88)
Word List Learning - immediate recall	Dementia	Heun, 1998[146]	All	13 (37/287)	287	≤3	0.82 (NR)	0.77 (NR)	NR	NR	0.871 (0.814, 0.928)
Word List Learning - immediate recognition false alarms	Dementia		All	13 (37/287)	287	≤1	0.23 (NR)	0.77 (NR)	NR	NR	0.515 (0.401, 0.629)
Word List Learning - immediate recognition hit	Dementia		All	13 (37/287)	287	≤6	0.57 (NR)	0.71 (NR)	NR	NR	0.670 (0.562, 0.778)
Word List Recognition	Dementia	Fuchs, 2012[142]	All	5 (21/423)	423	≤16	0.706 (0.489, 0.922)	0.933 (0.908, 0.957)	0.308 (0.163, 0.453)	0.987 (0.975, 0.998)	0.881 (0.784, 0.978)

* New study

Abbreviations: 7MS = 7 Minute Screen; AMT = Abbreviated Mental Test; AUC = area under the curve; CI = confidence interval; edu = education; FCR = Free and Cued Recall; FOME-abbreviated = Fuld Object Memory Evaluation – abbreviated version; M@T = Memory Alteration Test; MMblind = MMSE version for persons with visual impairment; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; n = number of participants analyzed; NPV = negative predictive value; NR = not reported; OT = Benton's Orientation Test; PPV = positive predictive value; SBT = Short Blessed Test; Sens = sensitivity; SLUMS = Veterans Affairs Saint Louis University Mental Status; Spec = specificity; TICS = Telephone Instrument for Cognitive Status; TICS-M = Telephone Interview for Cognitive Status modified; TYM = Test Your Memory

Table 6. Test Performance of Longer, Self-Administered Screening Instruments, by Instrument and Target Condition (KQ 2)

Test name	Target condition	Author, year	Screened Group	Percent (n/n) with condition	Total n	Cutoff	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
CAMCI	MCI	Saxton, 2009[171]	All	44 (228/524)	524	NA	0.86 (NR)	0.94 (NR)	NR	NR	NR
CAST	Dementia	Swearer, 2002[174]	All	17 (8/46)	46	≤33	0.88 (NR)	0.95 (NR)	NR	NR	NR
CIDS	Dementia	Waite, 1998[179]	All	28 (99/360)	360	6/7	0.89 (NR)	0.89 (NR)	NR	NR	0.91 (NR)
IQCODE	Dementia	Cruz-Orduna, 2011[132]	All	9 (15/160)	160	95/96	0.8000 (NR)	0.7671 (NR)	0.2609 (NR)	0.9739 (NR)	0.85 (0.76, 0.94)
		Jorm, 1996[151]	All	NR	NR	3.27/3.30	0.79 (NR)	0.65 (NR)	NR	NR	0.77 (NR)
		Morales, 1997[165]	Rural	13 (34/257)	160	86	0.83 (NR)	0.83 (NR)	0.45 (NR)	0.97 (NR)	NR
		Tokuhara, 2006[176]	All	7 (16/230)	230	3.5	0.875 (NR)	0.911 (NR)	0.424 (NR)	0.99 (NR)	NR
	Cognitive Impairment	Cruz-Orduna, 2011[132]	All	56 (90/160)	160	87/88	0.7111 (NR)	0.7429 (NR)	0.7805 (NR)	0.6667 (NR)	0.75 (0.67, 0.82)
		Jorm, 1996[151]	All	NR	NR	NR	NR	NR	NR	NR	0.75 (NR)
		Tokuhara, 2006[176]	All	17 (39/230)	230	3.5	0.739 (NR)	0.922 (NR)	0.515 (NR)	0.969 (NR)	0.87 (NR)
IQCODE-Short	Dementia	Ayalon, 2011[124]	All	32 (206/647)	647	>3	NR	NR	NR	NR	NR
		Jorm, 1996[151]	All	NR	NR	3.31/3.38	0.75 (NR)	0.68 (NR)	NR	NR	0.77 (NR)
	MCI	Ayalon, 2011[124]	All	29 (185/647)	441	>3	0.748 (NR)	0.690 (NR)	0.309 (NR)	0.251 (NR)	0.77 (NR)
	Cognitive Impairment	Ayalon, 2011[124]	All	60 (391/647)	647	>3	NR	NR	NR	NR	NR
		Jorm, 1996[151]	All	NR	NR	NR	NR	NR	NR	NR	0.74 (NR)
SCIDS	Dementia	Waite, 1998[179]	All	28 (99/360)	360	3/4	0.83 (NR)	0.87 (NR)	NR	NR	0.89 (NR)

Abbreviations: AUC = area under the curve; CAMCI = Computer Assessment of Mild Cognitive Impairment; CAST = Cognitive Assessment Screening Test; CI = confidence interval; CIDS = Concord Informant Dementia Scale; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; IQCODE-Short = Informant Questionnaire on Cognitive Decline in the Elderly - short version; MCI = mild cognitive impairment; n = number of participants analyzed; NPV = negative predictive value; NR = not reported; PPV = Positive predictive value; SCIDS = Short Concord Informant Dementia Scale

Table 7. Trial and Population Characteristics: Summary Across All Intervention Types (KQ 4 and 5)

Intervention Type	No. trials*	No. new studies (%)	No. randomized	No. studies (%) good quality	No. studies (%) conducted in U.S.‡	Median study duration, months (range)	Mean age, years†	No. studies (%) with condition	Mean baseline MMSE	% Female†
FDA-approved medication	48	6 (12)	22,431	4 (8)§	24 (50)	6 (3-48)	74	MCI: 4 (8) Dem: 44 (92)	19.5	55
Donepezil	18	1 (6)	6,209	0 (0)	11 (61)	6 (3-36)	73	MCI:3 (17) Dem: 15 (83)	22.0	52
Galantamine	10	1 (10)	7,464	0 (0)	5 (50)	6 (3-12)	74	Dem: 10 (100)	19.1	59
Rivastigmine	8	0 (0)	4,569	0 (0)	4 (50)	6 (3-6)	73	Dem: 8 (100)	18.4	57
Memantine	12	4 (33)	4,189	4 (33)	4 (33)	6 (3-48)	76	MCI: 1 (8) Dem: 11 (92)	17.8	49
Other medication or supplement	29	5 (17)	6,489	6 (21)	16 (55)	12 (3-48)	75	MCI: 5 (17) Dem: 23 (79) MCI/Dem: 1 (3)	22.3	52
Antihypertensives	1	1 (100)	385	0 (0)	0 (0)	4 (NA)	81	MCI: 1 (100)	26.0	59
HMG-CoA Reductase Inhibitors	4	0 (0)	1,153	0 (0)	3 (75)	12 (6-18)	74	Dem: 4 (100)	21.2	54
Dietary Supplements	14	3 (21)	3,777	4 (29)	7 (50)	12 (4-48)	75	MCI: 4 (29) Dem: 9 (64) MCI/Dem: 1 (7)	23.0	46
Gonadal Steroids	6	1 (17)	337	1 (17)	4 (67)	6 (3-12)	76	Dem: 6 (100)	20.1	95
NSAIDs	4	0 (0)	837	1 (25)	2 (50)	12 (12-12)	74	Dem: 4 (100)	20.1	56
Patient	61	39 (64)	7,847	13 (21)	13 (21)	6 (3-26)	76	MCI: 25 (41) Dem: 28 (46) MCI/Dem: 8 (13)	23.1	59
Cognitive Training, Stimulation, or Rehabilitation	28	17 (61)	3,212	5 (18)	6 (21)	6 (3-26)	76	MCI: 12 (43) Dem: 14 (50) MCI/Dem: 2 (7)	23.3	57
Exercise Interventions	21	14 (67)	2,831	6 (29)	4 (19)	6 (3-18)	75	MCI: 9 (43) Dem: 9 (43) MCI/Dem: 3 (14)	23.4	62
Multicomponent and Other Interventions	16	12 (75)	2,302	2 (12)	4 (25)	6 (3-24)	76	MCI: 7 (44) Dem: 6 (38) MCI/Dem: 3 (19)	22.8	59
Caregiver	88	33 (38)	14,880	13 (15)	40 (45)	9 (3-144)	78	MCI: 0 Dem: 84 (95) MCI/Dem: 4 (5)	17.6	56
Psychoeducation Interventions	58	24 (41)	9,139	6 (10)	28 (48)	6 (3-144)	78	Dem: 56 (97) MCI/Dem: 2 (3)	16.2	54

Table 7. Trial and Population Characteristics: Summary Across All Intervention Types (KQ 4 and 5)

Intervention Type	No. trials*	No. new studies (%)	No. randomized	No. studies (%) good quality	No. studies (%) conducted in U.S.‡	Median study duration, months (range)	Mean age, years†	No. studies (%) with condition	Mean baseline MMSE	% Female†
Care/Case Management	17	6 (35)	3,039	4 (24)	6 (35)	12 (6-24)	79	Dem: 15 (88) MCI/Dem: 2 (12)	19.8	58
Other Interventions	13	3 (23)	2,702	3 (23)	6 (46)	12 (3-24)	79	Dem: 13 (100)	19.1	57
Total	224	82 (37)	50,265	35 (16)	91 (41)	6 (3-144)	76	MCI: 33 (15) Dem: 178 (79) MCI/Dem: 13 (6)	19.9	56

* Studies can be counted in more than one intervention type.
† Values reported for patients (not caregivers)
‡ Including studies that were conducted in multiple countries, of which the US was one country.
§ 27 of these studies originated from a systematic review that was included in the previous review and were not quality rated again. For this table, they were all counted as "fair."

Abbreviations: Dem = dementia; FDA = US Food and Drug Administration; HMG-CoA = β-Hydroxy β-methylglutaryl-CoA; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; No. = number; NSAIDs = nonsteroidal anti-inflammatory drugs

Table 8. Intervention Characteristics: Summary Across All Intervention Types (KQ 4 and 5)

Intervention Category	Intervention Type	No. Trials*	Summary of Intervention Characteristics	Median (Range) of Intervention Duration, Months	Summary of Control Group Characteristics
AChEIs and Memantine (k=48)	Donepezil	18	Daily dosage ranged from 1 to 10 mg, with most trials using 5 to 10 mg per day.	6 (3-12)	Placebo controlled.
	Galantamine	10	Daily dosage ranged from 8 to 36 mg, with most trials used 16 to 24 mg per day.	6 (4-24)	Placebo controlled.
	Rivastigmine	8	Daily dosage of oral rivastigmine ranged from 1 to 12 mg, with considerable variability in daily dosage. Three trials examined the rivastigmine patch, with daily dosages of 9.5 mg, 12 mg and 17.4 mg.	6 (3-6)	Placebo controlled.
	Memantine	12	Daily dosage of 20 mg. In two trials, both intervention and control participants were also given galantamine (24 mg) or rivastigmine (9.5 mg).	6 (3-48)	Placebo controlled, except for one open-label study. Two studies gave all participants an additional AChEI.
Other Medications and Supplements (k=29)	Antihypertensive	1	Discontinuation of antihypertensive medication.	4 (NA)	Usual care consisting of continuation of antihypertensive treatment.
	HMG-CoA Reductase Inhibitors	4	Two studies of Atorvastatin (80 mg daily dosage), and two studies of Simvastatin (daily dosages ranged from 40-80 mg).	14 (6-18)	Placebo controlled, except for one study of Atorvastatin in which participants received 10 mg of Donepezil along with a placebo.
	NSAIDs	4	Four studies of different NSAIDs: One study of Celecoxib (400 mg daily dosage), one study of Ibuprofen (800 mg daily dosage), one study of Indomethacin (100 mg daily dosage) and omeprazole (20 mg daily dosage), and one study of Naproxen (440 mg daily dosage).	12 (12-12)	Placebo controlled, except for one study of Indomethacin that provided control participants with omeprazole (20 mg) along with a placebo, and another study of Ibuprofen that provided control participants with esomeprazole (20 mg).
	Gonadal Steroids	6	Four studies of estrogen (daily dosage ranging from 0.625-120 mg). One study of estrogen and progestin (1.5 mg daily dosage) and one study of testosterone (75 mg daily dosage).	9 (3-12)	Placebo controlled.
	Dietary Supplements	14	Four studies of B vitamins (variable combinations and daily dosages of B vitamins and folic acid). Three studies of vitamin E with daily dosages ranging from 1,000 to 2,000 IU.	10 (4-48)	Placebo controlled, except for four studies: One study of b vitamins provided participants with an AChEI along with a placebo. Two studies of omega-3 fatty acids provided participants with dietary supplements along with or included

Table 8. Intervention Characteristics: Summary Across All Intervention Types (KQ 4 and 5)

Intervention Category	Intervention Type	No. Trials*	Summary of Intervention Characteristics	Median (Range) of Intervention Duration, Months	Summary of Control Group Characteristics
			Six studies of omega-3 fatty acids (variable combinations and doses of DHA, EPA, and LA). One study of multivitamins (daily dosage: mecobalamin [0.5 mg] + multivitamin supplement that contained folic acid, pyridoxine HCl, ferrous [60 mg], nicotinamide [10 mg], calcium carbonate [250 mg], riboflavin [2 mg], thiamine mononitrate [3 mg], calcium pantothenate [1 mg], ascorbic acid [100 mg]).		in the placebo; one placebo containing safflower oil (containing 2.2 g linoleic acid) and the other containing isocaloric oil (1 g corn oil, 0.6 g linoleic acid). One study of vitamin E provided participants with a multivitamin containing 15 IU vitamin E along with a placebo.
Nonpharmacologic Patient-Level Interventions (k=61)	Cognitive Training, Cognitive Stimulation, or Cognitive Rehabilitation	28	Interventions that directly or indirectly targeted cognitive functioning through cognitive stimulation (engaging the person with CI in a range of activities and discussions aimed at general enhancement of cognitive and social functioning), cognitive training (guided practice on a set of standardized tasks designed to reflect particular cognitive functions such as memory, attention, or problem-solving), and/or cognitive rehabilitation (setting personally relevant goals related to performance in everyday life with patient and family and devising strategies to address these). Most cognitive-focused activities were group-based interventions, but the intensity of activities varied considerably from 1 day a week for 6 weeks to 5 days a week for up to two years with most sessions ranging from 45 to 90 minutes per session. Most common interventionists were trained psychologists or neuropsychologists. Four studies tested computer-based cognitive training programs.	3 (1-24)	Highly variable ranging from no intervention or waitlist (11 trials), usual care not including cognitive-focused activities (7 trials), brief interventions including psychoeducation and social support (3 trials), and “sham” cognitive-focused activities (7 trials).
	Exercise Interventions	21	Most exercise interventions included supervised group-based exercise sessions focused on aerobic activities, strength and resistance training, and/or balance training that took place in a community setting and were led by an exercise specialist. Four trials included individualized, supervised exercise sessions in the home or community setting whereas three trials encouraged self- or caregiver-guided exercises at home. Two trials evaluated the effectiveness of a group-based	6 (3-12)	Over half of the trials provided attention control groups including general health education relevant for older adults or brief interventions including supervised “sham” exercise sessions focused on stretching or toning (k=12). In the remaining trials, control groups received usual care with or without

Table 8. Intervention Characteristics: Summary Across All Intervention Types (KQ 4 and 5)

Intervention Category	Intervention Type	No. Trials*	Summary of Intervention Characteristics	Median (Range) of Intervention Duration, Months	Summary of Control Group Characteristics
			ballroom dancing intervention and one trial evaluated the impact of Tai Chi. Most interventions took place for 2-3 days per week for 30 minutes to 2 hours per session.		being offered the intervention at the end of the trial (k=9).
	Multicomponent and Other Interventions	16	Interventions in this group were all unique. Two trials included multicomponent interventions consisting of combined exercise with cognitive training or cognitive behavioral therapy and support groups. Three trials targeted patient well-being through diagnostic support and in-home counseling, group-based psychoeducation, and a self-management program and the remaining trial focused on vascular care through pharmacological and nonpharmacological interventions.	6 (2-24)	Highly variable, ranging from usual care provided by general practitioners (k=4); minimal or sham interventions (k=5); attention-control interventions (k=2); waitlist (k=4); or no intervention (k=1).
Caregiver and Caregiver-Patient Dyad Interventions (k=88)	Psychoeducation Interventions	58	Wide range of approaches with the most common format consisting of interventionists meeting individually with caregivers, dyads, or families, most commonly in participants' homes; however, a substantial number of interventions took place in group settings or were provided remotely through telephone counseling, computer-based programs or applications, videos, or a combination of these methods. Most interventions provided information about dementia and community resources and also included training in problem solving, communication techniques, and stress management. A variety of additional components were used, including peer or social support, supportive counseling, home safety assessments or information, occupational therapy, and environmental modifications. The interventionists were highly variable, including general educators or counselors, psychologists, nurses, occupational therapists, social workers, and hired and trained research staff. Most interventions involved multiple modes of delivery and included 10-15 sessions, with each session ranging from 30- to 120-minutes.	4 (1-24)	Highly variable, ranging from no intervention or waitlist (k=19); attention-control interventions (k=3); brief interventions (k=12) primarily consisting of basic educational materials about dementia caregiving (k=8), information on local resources (k=2), and some providing additional brief (10-15-min) telephone support calls with research staff or a social worker (k=3); minimal interventions (k=15) that were similar to the brief interventions, but had more intensive (20-60 min) telephone calls offering social support and tips for behavior management; and usual care interventions (k=39) consisting of standard care provided to dementia caregivers, which varied largely by country.
	Care/Case Management	17	Interventions included professional assistance to help arrange, implement, or facilitate services to meet a	12 (3-24)	Minimal interventions (k=5) involving enhanced usual care (k=3)

Table 8. Intervention Characteristics: Summary Across All Intervention Types (KQ 4 and 5)

Intervention Category	Intervention Type	No. Trials*	Summary of Intervention Characteristics	Median (Range) of Intervention Duration, Months	Summary of Control Group Characteristics
			patient's and family's needs and generally all provided assessment, advice and information, individualized treatment planning, caregiver psychoeducation and skills training, ongoing monitoring, and either referral or care coordination with outside social and health care services (such as occupational and physical therapy, respite care, personal care assistance, social, and social work). Interventionists varied, but most often included a nurse or other health provider serving as a "case manager" or "care coordinator."		and in-home visits by occupational therapists and primary care staff (k=2). The remaining control groups received usual care (k=12) consisting of standard care provided to dementia caregivers, which varied largely by country.
	Other Interventions	13	Interventions in this group were all unique. Interventions included: Physical activity counseling for the caregiver (k=3) provided in-person and remotely by educators/counselors or was entirely self-administered. Multicomponent dyadic intervention (k=2) delivered at home by psychologists or home health specialists. Social support only (k=3) delivered at home or community settings by peers and trained research staff. Assessment and treatment planning or multidisciplinary assessment only (k=3) delivered in medical settings by primary care staff. Provider training (k=1) delivered at home by nurses or psychologists. Transcendental meditation (k=1) delivered in community settings by a educators/counselors.	6 (2-24)	Variable, included attention-control (k=1) or no intervention (k=4); usual care (k=5) of standard care provided to dementia caregivers, which varied largely by country; a brief intervention (k=1) monthly mailings of general information and three brief emotional support telephone calls and minimal interventions (k=2), which varied by intervention type (exercise – pedometer provided; multidisciplinary assessment – biweekly telephone contact).

Abbreviations: AChEI = acetylcholinesterase inhibitor; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HMG-CoA = β-Hydroxy β-methylglutaryl-CoA; IU = International Unit; k = number of trials analyzed; LA = linoleic acid; mg = milligrams; No. = number; NSAIDs = nonsteroidal anti-inflammatory drugs

* Studies can be counted in more than one intervention type.

Table 9. Meta-Analyses Results: Summary Across All Intervention Types (KQ 4 and 5)

Main intervention category	Intervention type	Outcome	Pooled mean difference in change*	95% CI†	k	N	I^2	Tau
FDA Medications	Donepezil	GCF – ADAS-Cog	-2.13	-3.32 to -0.94	6	1,981	64.4	0.90
		GCF – MMSE	1.24	0.81 to 1.67	12	3,192	65.3	0.57
		GF (cont)	-0.24	-0.39 to -0.09	8	3,302	70.7	0.15
		GF (dichot)	1.33	1.07 to 1.66	9	2,440	77.4	0.23
		SAEs	1.18	0.99 to 1.40	12	4,045	0.0	0
		Withdrawals	1.88	1.54 to 2.29	13	4,124	8.8	0
	Galantamine	GCF – ADAS-Cog	-2.13	-2.94 to -1.32	9	3,786	65.9	0.84
		GCF – MMSE	NA	NA	1	1,765	NA	NA
		GF (cont)	NA	NA	1	126	NA	NA
		GF (dichot)	1.21	1.11 to 1.31	8	3,486	56.2	0.07
		SAEs	1.06	0.88 to 1.29	7	4,987	0.0	0
		Withdrawals	1.98	1.52 to 2.57	10	6,147	51.1	0.28
	Rivastigmine	GCF – ADAS-Cog	-2.43	-4.10 to -0.75	5	2,618	81.9	1.21
		GCF – MMSE	0.88	0.28 to 1.49	6	2,415	44.9	0.39
		GF (cont)	-0.14	-0.43 to 0.15	6	2,535	85.7	0.25
		GF (dichot)	1.49	1.13 to 1.98	5	1,934	61.4	0.16
		SAEs	1.15	0.87 to 1.52	6	2,619	10.4	0
		Withdrawals	2.21	1.43 to 3.42	8	3,131	57.0	0.38
	Memantine	GCF – ADAS-Cog	-0.88	-1.65 to -0.11	8	2,609	78.1	0.69
		GCF – MMSE	0.36	-0.31 to 1.04	5	1,217	33.2	0.27
		GF (cont)	-0.14	-0.33 to 0.05	5	1,396	32.9	0.09
		GF (dichot)	1.15	0.49 to 2.69	2	545	0.0	0
		SAEs	0.88	0.77 to 1.01	10	3,350	0.0	0
		Withdrawals	1.26	0.94 to 1.70	9	3,288	0.0	0
Nonpharm Patient Level	Cognitive Stimulation and Training	GCF – ADAS-Cog	-0.66	-1.60 to 0.29	8	842	0	0
		GCF – MMSE	1.33	0.29 to 2.37	15	1,384	91.1	1.91
	Exercise	GCF – ADAS-Cog	-1.05	-3.49 to 1.10	6	1,071	77.4	1.62
		GCF – MMSE	1.17	0.45 to 1.90	10	1,168	81.3	0.98
	Multicomponent and Other Interventions	GCF – ADAS-Cog	-1.66	-10.03 to 6.72	2	167	56.5	0.72
		GCF – MMSE	0.26	-0.54 to 1.00	8	1,238	30.3	0.55
Caregiver	Psychoeducation Interventions	CGR burden	-0.24	-0.36 to -0.13	27	2,776	50.2	0.20
		CGR depression	-0.26	-0.39 to -0.13	37	4,555	76.9	0.35
	Care or Case Management	CGR burden	-0.54	-0.96 to -0.12	8	1,215	82.9	0.45
		CGR depression	-0.13	-0.39 to 0.12	4	668	0.0	0
	Other Caregiver or Caregiver-Patient Dyad Interventions	CGR burden	-0.30	-2.26 to 1.36	5	459	89.6	1.36
		CGR depression	-0.00	-0.34 to 0.34	5	645	53.7	0.20

* For dichotomous outcomes, this represents a RR.

† For analyses with <10 studies, the REML method was used to calculate the CI

Table 9. Meta-Analyses Results: Summary Across All Intervention Types (KQ 4 and 5)

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; CGR = caregiver; CI = confidence interval; cont = continuous; dichot = dichotomous; FDA = US Food and Drug Administration; GCF = global cognitive function; GF = global function; k = number of trials analyzed; MMSE = Mini-Mental State Examination; n = number of participants analyzed; Nonpharm = nonpharmacological; SAEs = serious adverse events

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Table 10. AChEIs and Memantine: Study Characteristics, by Medication Type (KQ 4 and 5)

Medication	Author, year (Study name)	Quality	Country	N randomized	Population	Baseline MMSE, mean	Age, mean	Female, %
Donepezil	Black, 2003[184] (Donepezil 307 Vascular Dementia Study Group)	Fair-Good	US, GBR, AUS, CAN, DEU, IRL	603	Dem	21.8†	74	45
Donepezil	Burns, 1999[185]	Fair-Good	GBR, AUS, BEL, CAN, FRA, DEU, IRL, NZL, ZAF	818	Dem	20	72	57
Donepezil	Doody, 2009[186]	Fair	US	821	MCI	27.5	70	46
Donepezil	Feldman, 2001[187]	Fair-Good	AUS, CAN, FRA	290	Dem	11.8‡	74	61
Donepezil	Holmes, 2004[188]	Fair-Good	GBR	96	Dem	21	79	62
Donepezil	Ikeda, 2015*[189]	Fair	JPN	142	Dem	20.4	78	58
Donepezil	Krishnan, 2003[190]	Fair-Good	US	67	Dem	19.3	73	72
Donepezil	Mazza, 2006[191]	Fair-Good	ITA	51	Dem	18.7	68	54
Donepezil	Mohs, 2001[192]	Fair	US	431	Dem	17.1	75	63
Donepezil	Mori, 2012[193]	Fair	JPN	140	Dem	19.6	79	66
Donepezil	Petersen, 2005[194]	Fair	US, CAN	769	MCI	27.3	73	46
Donepezil	Rogers, 1996[196]	Fair-Good	US	161	Dem	18.8	72	60
Donepezil	Rogers, 1998[195] (Donepezil Study Group)	Fair-Good	US	468	Dem	19.5	74	64
Donepezil	Salloway, 2004[197] (Donepezil 401 MCI Study)	Fair-Good	US	269	MCI	27.4	72	42
Donepezil	Seltzer, 2004[198] (Donepezil 402 Study)	Fair-Good	US	153	Dem	24.2	74	54
Donepezil	Tune, 2003[199]	Fair-Good	US	28	Dem	21.1	73	75
Donepezil	Wilkinson, 2003[200] (Donepezil 308 Study)	Fair-Good	US, GBR, AUS, CAN, DEU, IRL	616	Dem	21.8	75	40
Donepezil	Winblad, 2001[211] (Donepezil Nordic Study Group)	Fair-Good	DNK, FIN, NLD, NOR, SWE	286	Dem	19.3	72	46
Galantamine	Auchus, 2007[202] (GAL-INT-26)	Fair	US	788	Dem	20.3	72	36
Galantamine	Brodaty, 2005[203] (GAL-INT-10)	Fair-Good	US, AUS, CAN, NZL, ZAF	971	Dem	18	76	64
Galantamine	Erkinjuntti, 2002[204] (GAL-INT-6)	Fair-Good	GBR, CAN, DNK, FIN, FRA, DEU, IRL, ISR, NLD, POL	592	Dem	20.5	75	47
Galantamine	Hager, 2014*[205]	Fair	CZE, FRA, DEU, GRC, ITA, LTU, RUS,	2045	Dem	19	73	65

Table 10. AChEIs and Memantine: Study Characteristics, by Medication Type (KQ 4 and 5)

Medication	Author, year (Study name)	Quality	Country	N randomized	Population	Baseline MMSE, mean	Age, mean	Female, %
			SVK, EST, LVA, SVN, ROU, UKR					
Galantamine	Raskind, 2000[206] (Galantamine USA - Study Group (GAL-USA-1))	Fair-Good	US	636	Dem	19.3	75	62
Galantamine	Rockwood, 2001[208] (GAL-INT-2)	Fair-Good	US, GBR, AUS, CAN, NZL, ZAF	386	Dem	19.7	75	56
Galantamine	Rockwood, 2006[207] (Video-Imaging Synthesis of Treated Alzheimer's disease (VISTA))	Fair	CAN	130	Dem	20.3	78	63
Galantamine	Tariot, 2000[209] (Galantamine USA - Study Group (GAL-USA-10))	Fair-Good	US	978	Dem	17.8	77	64
Galantamine	Wilcock, 2000[210] (Galantamine International-1-Group Study (GAL-INT-1))	Fair-Good	GBR, CAN, FIN, FRA, DEU, NLD, NOR, SWE	653	Dem	19.3	72	63
Galantamine	Wilkinson, 2001[211]	Fair-Good	GBR	285	Dem	18.6	74	58
Rivastigmine	Agid, 1998[212]	Fair-Good	GBR, AUT, BEL, CZE, DNK, FIN, FRA, DEU, IRL, NOR, SVK, SWE, CHE	402	Dem	NR	69	56
Rivastigmine	Ballard, 2008[213] (Vascular Dementia Trial studying Exelon (VantagE))	Fair	US, GBR, AUT, CAN, FRA, DEU, ITA, KOR, RUS, ESP, TWN	710	Dem	19.2	73	38
Rivastigmine	Corey-Bloom, 1998[214]	Fair-Good	US	699	Dem	19.7	74	61
Rivastigmine	Feldman, 2007[215] (Study 304)	Fair	GBR, AUS, CAN, IRL, ITA, ZAF	678	Dem	18.6	71	59
Rivastigmine	McKeith, 2000[216]	Fair-Good	GBR, ITA, ESP	120	Dem	17.8	74	43
Rivastigmine	Mok, 2007[217]	Fair	HKG	40	Dem	13.2	75	60
Rivastigmine	Rosler, 1999[218] (B303 Exelon Study)	Fair-Good	US, AUT, CAN, FRA, DEU, CHE	725	Dem	19.9	72	59
Rivastigmine	Winblad, 2007[219] (Investigation of transDermal Exelon in ALzheimer's disease (IDEAL))	Fair	US, CHL, CZE, DNK, FIN, DEU, GTM, ISR, ITA, KOR, MEX, NOR, PER, POL, PRT, RUS, SVK, SWE, TWN, VEN	1195	Dem	16.5	74	66

Table 10. AChEIs and Memantine: Study Characteristics, by Medication Type (KQ 4 and 5)

Medication	Author, year (Study name)	Quality	Country	N randomized	Population	Baseline MMSE, mean	Age, mean	Female, %
Memantine	Bakchine, 2008[220]	Good	GBR, AUT, BEL, DNK, FIN, FRA, GRC, LTU, NLD, POL, ESP, SWE	470	Dem	18.7	74	63
Memantine	Choi, 2011*[221]	Fair	KOR	172	Dem	16.6	75	80
Memantine	Dysken, 2014*[222] (TEAM-AD VA)	Good	US	613	Dem	21	79	3
Memantine	Ferris, 2007[223]	Fair	US	60	MCI	28.8	67	65
Memantine	Herrmann, 2013*[224]	Fair	CAN	369	Dem	11.8	75	58
Memantine	Orgogozo, 2002[225] (MMM 300)	Fair-Good	BEL, FRA, CHE	321	Dem	16.9	76	47
Memantine	Peskind, 2006[226] (MEM-MD-10)	Fair-Good	US	403	Dem	17.3	78	59
Memantine	Peters, 2015*[227]	Fair	DEU	226	Dem	22.2	72	64
Memantine	Porsteinsson, 2008[228] (MEM-MD-12)	Good	US	433	Dem	16.8	75	52
Memantine	Saxton, 2012[229] (MEM-MD-71)	Good	AUS, NZL, ZAF	265	Dem	15.8	75	58
Memantine	Wilcock, 2002[230] (MMM500)	Fair-Good	GBR	579	Dem	17.6	77	48
Memantine	Wilkinson, 2012[231]	Fair	GBR, FRA, DEU, CHE	278	Dem	16.9	74	57
Any AChEI	Gill, 2009[232]	Good	CAN	81,302	Dem	NR	80	61
Any AChEI	Hernandez, 2009[233]	Good	US	11,328	Dem	NR	74	4
Any AChEI	Thavorn, 2014[234]	Fair	CAN	97,446	Dem	NR	82	64

* New Study
† Least squares mean
‡ Standardized MMSE

Abbreviations: AUS = Australia; AUT = Austria; BEL = Belgium; CAN = Canada; CHE = Switzerland; CZE = Czech Republic; Dem = Dementia; DEU = Germany; DNK = Denmark; ESP = Spain; EST = Estonia; FIN = Finland; FRA = France; GBR = Great Britain/United Kingdom; GRC = Greece; GTM = Guatemala; HKG = Hong Kong; IRL = Ireland; ISR = Israel; ITA = Italy; JPN = Japan; KOR = Korea; LEADe = Lipitor's Effect in Alzheimer's; Dementia; LVA = Latvia; LTU = Lithuania; MCI = mild cognitive impairment; MEX = Mexico; MMSE = Mini-Mental State Examination; N = number of participants; NLD = Netherlands; NOR = Norway; NR = not reported; NZL = New Zealand; PER = Peru; POL = Poland; PRT = Portugal; ROU = Romania; RUS = Russia; SVK = Slovakia; SVN = Slovenia; SWE = Sweden; TWN = Taiwan; UKR = Ukraine; VEN = Venezuela; ZAF = South Africa

Table 11. AChEIs and Memantine: Interventions Characteristics, by Medication Type (KQ 4 and 5)

Author, year	Country	Pop cat	Medication (total daily dose)	Duration, weeks	Intervention details	CG description
Black, 2003[184] Fair-Good	US, GBR, AUS, CAN, DEU, IRL	Dem	IG1: Donepezil (10 mg) IG2: Donepezil (5 mg)	24	IG1: Started at 5 mg qd and increased to 10 mg qd after 4 weeks IG2: 5 mg qd	Placebo
Burns, 1999[185] Fair-Good	GBR, AUS, BEL, CAN, FRA, DEU, IRL, NZL, ZAF	Dem	IG1: Donepezil (10 mg) IG2: Donepezil (5 mg)	24	IG1: Started with 5 mg qd and increased 10 mg qd after 7 days IG2: 5 mg qd	Placebo
Doody, 2009[186] Fair	US	MCI	Donepezil (5-10 mg)	48	5 mg qd for 6 weeks followed by 10 mg qd for remainder of 28 weeks; allowed to reduce down to 5 mg qd if tolerability issues.	Placebo
Feldman, 2001[187] Fair-Good	AUS, CAN, FRA	Dem	Donepezil (10 mg)	24	Started with 5 mg qd for first 28 days, then increased dose to 10 mg qd. Study medication could be reduced to 5 mg qd at any time during study to improve tolerability	Placebo
Holmes, 2004[188] Fair-Good	GBR	Dem	Donepezil (10 mg)	24	Run-in was open label phase with 5 mg qd, for 6 weeks, then 10 mg qd for further 6 weeks, then patients randomized to placebo or 10 mg qd for further 12 weeks.	Placebo
Ikeda, 2015*[189] Fair	JPN	Dem	IG1: Donepezil (10 mg) IG2: Donepezil (5 mg)	12	IG1: Treatment began with 3 mg qd for 2 weeks then dose increased to 5 mg qd, then to 10 mg qd at week 6. IG2: Started at 3 mg qd for 2 weeks, then dose increased to 5 mg qd.	Placebo
Krishnan, 2003[190] Fair-Good	US	Dem	Donepezil (10 mg)	24	Started at 5 mg qd for first 28 days, then 10 mg qd thereafter	Placebo
Mazza, 2006[191] Fair-Good	ITA	Dem	Donepezil (5 mg)	24	5 mg qd	Placebo
Mohs, 2001[192] Fair	US	Dem	Donepezil (10 mg)	54	Started at 5 mg qd for first 28 days and 10 mg qd thereafter	Placebo
Mori, 2012[193] Fair	JPN	Dem	IG1: Donepezil (10 mg) IG2: Donepezil (5 mg) IG3: Donepezil (3 mg)	12	IG1: Titrated from 3 mg qd for 2 weeks, 5 mg qd for 4 weeks and then 10 mg qd for 6 weeks. IG2: Titrated from 3 mg qd for 2 weeks up to 5 mg qd. IG3: 3 mg qd	Placebo
Petersen, 2005[194] Fair	US, CAN	MCI	Donepezil (10 mg)	156	Started at 5 mg qd, then increased to 10mg qd after 6 weeks	Placebo + multivitamin containing 15 IU Vitamin E

Table 11. AChEIs and Memantine: Interventions Characteristics, by Medication Type (KQ 4 and 5)

Author, year	Country	Pop cat	Medication (total daily dose)	Duration, weeks	Intervention details	CG description
Rogers, 1996[196] Fair-Good	US	Dem	IG1: Donepezil (5 mg) IG2: Donepezil (3 mg) IG3: Donepezil (1 mg)	12	IG1: 5 mg qd for 12 weeks followed by 2 week placebo washout period IG2: 3 mg qd for 12 weeks followed by 2 week placebo washout period IG3: 1 mg qd for 12 weeks followed by 2 week placebo washout period	Placebo
Rogers, 1998[195] Fair-Good	US	Dem	IG1: Donepezil (10 mg) IG2: Donepezil (5 mg)	15	IG1: Started at 5 mg qd during week 1 and increased to 10 mg qd weeks 2-12, followed by placebo washout weeks 13-15 IG2: 5 mg qd for 12 weeks followed by placebo washout weeks 13-15	Placebo
Salloway, 2004[197] Fair-Good	US	MCI	Donepezil (10 mg)	24	Started at 5 mg qd and increased to 10 mg qd after 42 days	Placebo
Seltzer, 2004[198] Fair-Good	US	Dem	Donepezil (10 mg)	24	Started at 5 mg and increased to 10 mg qd after 6 weeks	Placebo
Tune, 2003[199] Fair-Good	US	Dem	Donepezil (10 mg)	24	Started at 5 mg qd for first 28 days and then increased to 10 mg qd after 28 days	Placebo
Wilkinson, 2003[200] Fair-Good	US, GBR, AUS, CAN, DEU, IRL	Dem	IG1: Donepezil (10 mg) IG2: Donepezil (5 mg)	24	IG1: Started at 5 mg qd and increased to 10 mg qd after 28 days IG2: 5 mg qd	Placebo
Winblad, 2001[201] Fair-Good	DNK, FIN, NLD, NOR, SWE	Dem	Donepezil (10 mg)	52	Started on 5 mg qd for 28 days, and then 10 mg qd. If required, a dose reduction to 5 mg qd was permitted.	Placebo
Auchus, 2007[202] Fair	US	Dem	Galantamine (16-24 mg)	26	4 mg bid for 4 weeks followed by 8 mg bid for 4 weeks; dosage could be maintained or increased to 12 mg bid (after additional 4 weeks, maintained or reduced to 8 mg bid for tolerability). Mean (SD) dose over entire treatment, 16.4 (3.98) mg qd	Placebo
Brodaty, 2005[203] Fair-Good	US, AUS, CAN, NZL, ZAF	Dem	IG1: Galantamine (16-24 mg) IG2: Galantamine (16-24 mg)	26	IG1: Run-in period: placebo for 4 weeks; Titrated from initial dosage of 4 mg bid for weeks 1 through 4; weeks 5 through 8 titrated to 8 mg bid; after 8 weeks, 8- or 12-mg bid IG2: Run-in period: placebo for 4 weeks; Titrated from initial dosage of 8 mg qd in morning with placebo in the	Placebo

Table 11. AChEIs and Memantine: Interventions Characteristics, by Medication Type (KQ 4 and 5)

Author, year	Country	Pop cat	Medication (total daily dose)	Duration, weeks	Intervention details	CG description
					evening for weeks 1 through 4; weeks 5 through 8 titrated to 16 mg qd in morning with placebo in evening; after 8 weeks, 16- or 24-mg qd in morning	
Erkinjuntti, 2002[204] Fair-Good	GBR, CAN, DNK, FIN, FRA, DEU, IRL, ISR, NLD, POL	Dem	Galantamine (24 mg)	26	After 4 weeks placebo run-in period, started 4 mg qd in the first week, with weekly increments of 4 mg qd until reached 24 mg qd in week 6.	Placebo
Hager, 2014*[205] Fair	CZE, FRA, DEU, GRC, ITA, LTU, RUS, SVK, EST, LVA, SVN, ROU, UKR	Dem	Galantamine (24 mg)	104	12 week titration period started at 8 mg qd, then increased to 16 mg qd, and up to 24 mg qd. Galantamine maintained at stable dose of at least 16 mg qd for next 21 months.	Placebo
Raskind, 2000[206] Fair-Good	US	Dem	IG1: Galantamine (24 mg) IG2: Galantamine (32 mg)	26	IG1: Following a 4-week run-in period, started at 8 mg qd for the first week, followed by 16 mg qd in the second and 24 mg qd in the third week. In the fourth week, continued to receive the 24 mg qd dose for an additional 5 months. IG2: Following a 4-week run-in period, started at 8 mg qd for the first week, followed by 16 mg qd in the second and 24 mg qd in the third week. In the fourth week, dose was increased to 32 mg qd dose for an additional 5 months.	Placebo
Rockwood, 2001[208] Fair-Good	US, GBR, AUS, CAN, NZL, ZAF	Dem	Galantamine (24-32 mg)	12	Started at 4 mg bid for 1 week, increased to 8 mg bid for the 2nd week and 12 mg bid for the 3rd week; during week 4 increased to 16 mg bid at the discretion of the investigator based on tolerance and by the end of the 4th week, the investigator could red	Placebo
Rockwood, 2006[207] Fair	CAN	Dem	Galantamine (16-24 mg)	16	16 to 24 mg qd; 1 tablet bid with food. Titrated from 8 mg qd (4 mg bid) for 4 weeks; 16 mg qd for another 4 weeks. At end of 8 weeks, dose could be increased to 24 mg qd depending on tolerability. At 12 weeks, dose could be reduced to 16 mg qd.	Placebo
Tariot, 2000[209] Fair-Good	US	Dem	IG1: Galantamine (24 mg) IG2: Galantamine (16 mg) IG3: Galantamine (8 mg)	21	IG1: Started at 4 mg bid for 4 weeks, then 8 mg bid for 4 weeks, and then maintenance dose at 12 mg bid from weeks 9 to 21 IG2: Started at 4 mg bid for 4 weeks followed by 8 mg bid for 17 weeks	Placebo

Table 11. AChEIs and Memantine: Interventions Characteristics, by Medication Type (KQ 4 and 5)

Author, year	Country	Pop cat	Medication (total daily dose)	Duration, weeks	Intervention details	CG description
					IG3: Started at 4 mg bid for 4 weeks followed by 8 mg bid for 17 weeks	
Wilcock, 2000[210] Fair-Good	GBR, CAN, FIN, FRA, DEU, NLD, NOR, SWE	Dem	IG1: Galantamine (24 mg) IG2: Galantamine (32 mg)	26	IG1: Started at 4 mg bid for one week, increasing to 8 mg bid for second week, and in the third week increased to 12 mg bid which was continued for rest of the study (5 months). IG2: Started at 4 mg bid for one week, increasing to 8 mg bid for second week, increasing to 12 mg bid for the third week, and in the fourth week increased to 16 mg bid which was continued rest of the study (5 months).	Placebo
Wilkinson, 2001[211] Fair-Good	GBR	Dem	IG1: Galantamine (24 mg) IG2: Galantamine (36 mg) IG3: Galantamine (18 mg)	12	IG1: After a 2-week washout period, started at 4 mg bid; increased progressively at 2- to 3-day intervals until the target dosage level of 8 mg tid was achieved after 8 days - then followed by 10 weeks of continuous fixed medication. IG2: After a 2-week washout period, started 4 mg bid; increased progressively at 2- to 3-day intervals until the target dosage level of 12 mg tid was achieved after 14 days - then followed by 10 weeks of continuous fixed medication. IG3: After a 2-week washout period, started at 4 mg bid; increased progressively at 2- to 3-day intervals until the target dosage level of 6 mg tid was achieved after 5 days - then followed by 10 weeks of continuous fixed medication.	Placebo
Agid, 1998[212] Fair-Good	GBR, AUT, BEL, CZE, DNK, FIN, FRA, DEU, IRL, NOR, SVK, SWE, CHE	Dem	IG1: Rivastigmine (6 mg) IG2: Rivastigmine (4 mg)	13	IG1: Started at 1 mg bid and titrated to 2.5 mg bid for 3 weeks, then maintained 3 mg bid for 10 weeks. IG2: Started at 1 mg bid and titrated to 1.5 mg bid for 1 week, then maintained 2 mg bid for 12 weeks.	Placebo
Ballard, 2008[213] Fair	US, GBR, AUT, CAN, FRA, DEU, ITA, KOR, RUS, ESP, TWN	Dem	Rivastigmine (3-12 mg)	24	Treatment began with 1.5 mg bid and doses were increased by 1.5 mg bid at every 4 week interval over 16 weeks. The highest well-tolerated dose was maintained for the duration of the study. Mean dose by the end of the study was 9.6 mg qd.	Placebo

Table 11. AChEIs and Memantine: Interventions Characteristics, by Medication Type (KQ 4 and 5)

Author, year	Country	Pop cat	Medication (total daily dose)	Duration, weeks	Intervention details	CG description
Corey-Bloom, 1998[214] Fair-Good	US	Dem	IG1: Rivastigmine (6-12 mg) IG2: Rivastigmine (1-4 mg)	26	IG1: Started at 3 mg bid and dose was titrated weekly to 6 mg bid during weeks 1-7; and during flexible dose maintenance phase weeks 8-26, doses increased within the assigned range (6-12 mg qd) until maximum dose or maximum tolerated dose was achieved. IG2: Started at 0.5 mg bid and dose was titrated weekly to 2 mg bid during weeks 1-7; and during flexible dose maintenance phase weeks 8-26, doses increased within the assigned range (1-4 mg qd) until maximum dose or maximum tolerated dose was achieved.	Placebo
Feldman, 2007[215] Fair	GBR, AUS, CAN, IRL, ITA, ZAF	Dem	IG1: Rivastigmine (9.6 mg) IG2: Rivastigmine (8.9 mg)	26	IG1: 2-12 mg qd given tid, mean 9.6 mg qd IG2: 2-12 mg qd given bid, mean 8.9 mg qd	Placebo
McKeith, 2000[216] Fair-Good	GBR, ITA, ESP	Dem	Rivastigmine (12 mg)	20	Started with 1.5 mg bid rivastigmine or placebo; doses escalated by 1.5 mg bid for a max of 2 weeks at each dose until 6 mg bid or maximum well tolerated maintenance dose reached. Titration lasted up to 8 weeks.	Placebo
Mok, 2007[217] Fair	HKG	Dem	Rivastigmine (6 mg)	26	Started at 1.5 mg bid and increased to 3 mg bid after 4 weeks	Placebo
Rosler, 1999[218] Fair-Good	US, AUT, CAN, FRA, DEU, CHE	Dem	IG1: Rivastigmine (6-12 mg) IG2: Rivastigmine (1-4 mg)	26	IG1: Dosages increased weekly in steps of up to 1.5 mg qd during weeks 1-12; must be within target range by week 7. Decreases were not permitted during the first 12 weeks. Mean dose 10.4 mg qd by the end of the study. IG2: Dosages increased weekly in steps of up to 1.5 mg qd during weeks 1-12; must be within target range by week 7. Decreases were not permitted during the first 12 weeks. Mean dose 3.7 mg qd by the end of the study.	Placebo
Winblad, 2007[219] Fair	US, CHL, CZE, DNK, FIN, DEU, GTM, ISR, ITA, KOR, MEX, NOR, PER, POL, PRT, RUS, SVK, SWE, TWN, VEN	Dem	IG1: Rivastigmine (12 mg) IG2: Rivastigmine (17.4 mg) IG3: Rivastigmine (9.5 mg)	24	IG1: 12 mg qd capsule titrated from 3 mg qd to maximum 12 mg qd in 4-week steps over 16 weeks. IG2: 20 square centimeter patch (17.4 milligrams/24 hours), titrated in 5 square cm patches to the target dose in 4-week steps over 16 weeks. Patients maintained at their highest tolerated dose.	Placebo

Table 11. AChEIs and Memantine: Interventions Characteristics, by Medication Type (KQ 4 and 5)

Author, year	Country	Pop cat	Medication (total daily dose)	Duration, weeks	Intervention details	CG description
					IG3: 10 square centimeter patch (9.5 milligrams/24 hours), titrated in 5 square cm patches to the target dose in 4-week steps over 16 weeks. Patients maintained at their highest tolerated dose.	
Bakchine, 2008[220] Good	GBR, AUT, BEL, DNK, FIN, FRA, GRC, LTU, NLD, POL, ESP, SWE	Dem	Memantine (20 mg)	24	Three week up titration then 21 weeks of 20 mg qd (10 mg bid)	Placebo
Choi, 2011*[221] Fair	KOR	Dem	Memantine (20 mg) + Rivastigmine (9.5 mg)	16	Starting at baseline (end of run-in period for rivastigmine, considered as week 0, titrated in 5 mg weekly increments from a starting dose of 5 mg qd to 20 mg qd at week 4. Memantine use concurrent with 10 cm^2 (9.5 mg qd) Rivastigmine patch.	Rivastigmine (9.5 mg)
Dysken, 2014*[222] Good	US	Dem	Memantine (20 mg)	208	Titrated over 4 weeks to maintenance dosage of 10 mg bid.	Placebo
Ferris, 2007[223] Fair	US	MCI	Memantine (20 mg)	12	Titrated from 10 mg (5 mg bid) to 20 mg (10 mg bid) daily over a 1 month period.	Placebo
Herrmann, 2013*[224] Fair	CAN	Dem	Memantine (20 mg)	24	Titrated in 5 mg weekly increments from starting dose of 5 mg qd to 20 mg qd beginning at Week 4	Placebo
Orgogozo, 2002[225] Fair-Good	BEL, FRA, CHE	Dem	Memantine (20 mg)	28	2-week placebo run-in period. Started at 5 mg qd at week 1, 10 mg qd at week 2, and 15 mg qd at week 3; patients received 20mg qd of memantine for remainder of followup	Placebo
Peskind, 2006[226] Fair-Good	US	Dem	Memantine (20 mg)	24	After 7-14 day single-blind placebo lead-in, started at 5 mg qd and titrated in 5-mg weekly increments to final dose of 20 mg qd (administered as two 5-mg tablets bid) on day 22	Placebo
Peters, 2015*[227] Fair	DEU	Dem	Memantine (20 mg)	52	Memantine titrated over 4 weeks in steps of 5 mg qd up to 20 mg qd.	Placebo + Galantamine (24 mg qd)
Porsteinsson, 2008[228] Good	US	Dem	Memantine (20 mg)	24	20 mg qd (four 5 mg tablets qd at bedtime); initial dose of 5 mg qd titrated in 5 mg weekly increments until reached final dose on day 22. Transient-dose adjustments permitted during weeks 3-8 for subjects with tolerability issues	Placebo
Saxton, 2012[229] Good	AUS, NZL, ZAF	Dem	Memantine (20 mg)	12	Titrated in weekly increments of 5 mg reaching maximum target dose of 10 mg bid by week 4.	Placebo

Table 11. AChEIs and Memantine: Interventions Characteristics, by Medication Type (KQ 4 and 5)

Author, year	Country	Pop cat	Medication (total daily dose)	Duration, weeks	Intervention details	CG description
Wilcock, 2002[230] Fair-Good	GBR	Dem	Memantine (20 mg)	28	Single blind run-in using placebo only for 2 weeks and double-blind treatment phase after randomization (28 weeks). Patients titrated up to daily dose of 20 mg starting at 5 mg daily with weekly increments of 5 mg,	Placebo
Wilkinson, 2012 Fair[231]	GBR, FRA, DEU, CHE	Dem	Memantine (20 mg)	52	20 mg qd. Titrated up from 5 mg qd to target dose of 20 mg qd (increased 5 mg qd once a week during a 4 week dose escalation period); mean memantine dose ranging from 8.7-21.6	Placebo

* New Study

Abbreviations: AUS = Australia; AUT = Austria; BEL = Belgium; bid = twice a day; CAN = Canada; CG = control group; CHE = Switzerland; cm^2 = square centimeter; CZE = Czech Republic; Dem = Dementia; DEU = Germany; DNK = Denmark; ESP = Spain; EST = Estonia; FIN = Finland; FRA = France; GBR = Great Britain/United Kingdom; GRC = Greece; GTM = Guatemala; HKG = Hong Kong; IG = intervention group; IRL = Ireland; ISR = Israel; ITA = Italy; IU = International Unit; JPN = Japan; KOR = Korea; LVA = Latvia; LTU = Lithuania; MCI = mild cognitive impairment; MEX = Mexico; mg = milligram; MMSE = Mini-Mental State Examination; N = number of participants; NLD = Netherlands; NOR = Norway; NZL = New Zealand; PER = Peru; POL = Poland; PRT = Portugal; Pop cat = population category; qd = once a day; ROU = Romania; RUS = Russia; SVK = Slovakia; SVN = Slovenia; SWE = Sweden; tid = three times a day; TWN = Taiwan; UKR = Ukraine; VEN = Venezuela; ZAF = South Africa

Table 12. AChEIs and Memantine: Summary of Results, by Medication Type (KQ 4 and 5)

Medication	Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-specific Cognitive Function	Physical Function	Neuro Symptoms	Other
Donepezil	Black, 2003[184] Fair-Good	Dem	603	74	6	IG1: ↔ (CIBIC+[D]), ↑ (CDR-SB) IG2: ↔ (CIBIC+[D]), ↔ (CDR-SB)	IG1: ↑ (ADAS-Cog), ↑ (MMSE) IG2: ↑ (ADAS-Cog), ↑ (MMSE)	NR	IG1: ↔ (ADL/IADL), ↔ IADL IG2: ↔ (ADL/IADL), ↑ IADL	NR	NR
Donepezil	Burns, 1999[185] Fair-Good	Dem	818	72	6	IG1: ↑ (CIBIC+), ↑ (CDR-SB) IG2: ↑ (CIBIC+), ↑ (CDR-SB)	IG1: ↑ (ADAS-Cog) IG2: ↑ (ADAS-Cog)	NR	IG1: ↑ (ADL/IADL) IG2: ↑ (ADL/IADL)	NR	NR
Donepezil	Doody, 2009[186] Fair	MCI	821	70	11	↔ (CIBIC+), ↔ (CDR-SB)	↑ (ADAS-Cog), ↔ (MMSE)	↔ (Attention)	NR	↔	NR
Donepezil	Feldman, 2001[187] Fair-Good	Dem	291	74	6	↑ (CIBIC+[D])	↑ (MMSE)	NR	↑ (ADL/IADL), ↑ (ADL), ↑ (IADL)	↑	NR
Donepezil	Holmes, 2004[188] Fair-Good	Dem	96	79	3	NR	↑ (MMSE)	NR	NR	↑	↑ (CGR Burden)
Donepezil	Ikeda, 2015*[189] Fair	Dem	142	78	3	NR	IG1: ↑ (MMSE) IG2: ↔ (MMSE)	NR	NR	IG1: ↔ IG2: ↔	IG1: ↔ (CGR Burden) IG2: ↔ (CGR Burden)
Donepezil	Krishnan, 2003[190] Fair-Good	Dem	67	73	6	NR	↑ (ADAS-Cog)	NR	NR	NR	NR
Donepezil	Mazza, 2006[191] Fair-Good	Dem	76	68	6	↑ (CGI Item 2)	↔ (MMSE)	↑ (Attention)	NR	NR	NR
Donepezil	Mohs, 2001[192] Fair	Dem	431	75	12	↑ (CDR/ADL/IADL[D])	NR	NR	NR	NR	NR
Donepezil	Mori, 2012[193] Fair	Dem	140	79	3	IG1: ↑ (CIBIC+[D]) IG2: ↔ (CIBIC+[D]) IG3: ↔ (CIBIC+[D])	IG1: ↑ (MMSE) IG2: ↑ (MMSE) IG3: ↑ (MMSE)	IG1: ↔ (Attention), ↑ (EF), ↔ (Language) IG2: ↑ (Attention), ↑ (EF), ↔‡ (Language)	NR	IG1: ↑ IG2: ↑ IG3: ↔	IG1: ↑ (CGR Burden) IG2: ↔ (CGR Burden) IG3: ↔ (CGR Burden)

Table 12. AChEIs and Memantine: Summary of Results, by Medication Type (KQ 4 and 5)

Medication	Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-specific Cognitive Function	Physical Function	Neuro Symptoms	Other
								IG3: ↑ (Attention), ↔ (EF), ↔ (Language)			
Donepezil	Petersen, 2005[194] Fair	MCI	769	73	36	↔ (CDR-SB), ↔† (GDS)	↔ (ADAS-Cog), ↔ (MMSE)	↔ (EF), ↔‡ (Language), ↔‡ (Memory)	↔ (IADL)	NR	↑ (Dementia Incidence)
Donepezil	Rogers, 1996[196] Fair-Good	Dem	161	72	3	IG1: ↔ (CDR-SB) IG2: ↔ (CDR-SB) IG3: ↔ (CDR-SB)	IG1: ↑ (ADAS-Cog), ↔ (MMSE) IG2: ↑ (ADAS-Cog), ↔ (MMSE) IG3: ↔ (ADAS-Cog), ↔ (MMSE)	NR	IG1: ↔ (ADL) IG2: ↔ (ADL) IG3: ↔ (ADL)	NR	NR
Donepezil	Rogers, 1998[195] Fair-Good	Dem	468	74	4	IG1: ↑ (CIBIC+[D]), ↔ (CDR-SB) IG2: ↑ (CIBIC+[D]), ↔ (CDR-SB)	IG1: ↑ (ADAS-Cog), ↑ (MMSE) IG2: ↑ (ADAS-Cog), ↑ (MMSE)	NR	NR	NR	NR
Donepezil	Salloway, 2004[197] Fair-Good	MCI	270	72	6	↔ (CGIC-MCI [D])	↑ (ADAS-Cog), ↔ (ADAS-Cog [D])	↔ (Attention), ↔ (Memory)	NR	NR	NR
Donepezil	Seltzer, 2004[198] Fair-Good	Dem	153	74	6	NR	↑ (ADAS-Cog), ↑ (ADAS-Cog [D]), ↑ (MMSE)	↔ (Memory)	NR	NR	NR
Donepezil	Tune, 2003[199] Fair-Good	Dem	28	73	6	NR	↔ (ADAS-Cog)	NR	NR	↔	NR
Donepezil	Wilkinson, 2003[200] Fair-Good	Dem	616	75	6	IG1: ↑ (CIBIC+[D]), ↑ (CDR-SB) IG2: ↑ (CIBIC+[D]), ↑ (CDR-SB)	IG1: ↑ (ADAS-Cog), ↑ (MMSE) IG2: ↑ (ADAS-Cog), ↑ (MMSE)	NR	IG1: ↔ (ADL/IADL) IG2: ↔ (ADL/IADL)	NR	NR
Donepezil	Winblad, 2001[201] Fair-Good	Dem	286	72	12	↔ (GBS), ↑ (GDS[D])	↑ (MMSE)	NR	↑ (ADL/IADL)	NR	NR
Galantamine	Auchus, 2007[202] Fair	Dem	788	72	6	↔ (CIBIC+[D])	↑ (ADAS-Cog)	NR	↔ (ADL/IADL)	NR	NR
Galantamine	Brodaty, 2005[203] Fair-Good	Dem	971	76	6	IG1: ↑ (CIBIC+[D]) IG2: ↔ (CIBIC+[D])	IG1: ↑ (ADAS-Cog) IG2: ↑ (ADAS-Cog)	NR	IG1: ↑ (ADL/IADL) IG2: ↑ (ADL/IADL)	IG1: ↔ IG2: ↔	NR

Table 12. AChEIs and Memantine: Summary of Results, by Medication Type (KQ 4 and 5)

Medication	Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-specific Cognitive Function	Physical Function	Neuro Symptoms	Other
Galantamine	Erkinjuntti, 2002[204] Fair-Good	Dem	592	75	6	↑ (CIBIC+[D])	↑ (ADAS-Cog), ↑ (ADAS-Cog [D])	NR	↑ (ADL/IADL)	↑	NR
Galantamine	Hager, 2014*[206] Fair	Dem	2051	73	12	NR	↑ (MMSE)	NR	↑ (ADL/IADL)	NR	NR
Galantamine	Raskind, 2000[206] Fair-Good	Dem	636	75	6	IG1: ↑ (CIBIC+[D]) IG2: ↔ (CIBIC+[D])	IG1: ↑ (ADAS-Cog) IG2: ↑ (ADAS-Cog)	NR	NR	NR	NR
Galantamine	Rockwood, 2001[208] Fair-Good	Dem	386	75	3	↑ (CIBIC+[D])	↑ (ADAS-Cog), ↔ (ADAS-Cog [D])	NR	↑ (ADL/IADL)	↔	NR
Galantamine	Rockwood, 2006[207] Fair	Dem	130	78	4	↔ (CIBIC+)	↑ (ADAS-Cog)	NR	↔ (ADL/IADL)	NR	NR
Galantamine	Tariot, 2000[209] Fair-Good	Dem	978	77	5	↑ (CIBIC+[D])	IG1: ↑ (ADAS-Cog), ↑ (ADAS-Cog [D]) IG2: ↑ (ADAS-Cog), ↑ (ADAS-Cog [D]) IG3: ↔ (ADAS-Cog), ↔ (ADAS-Cog [D])	NR	IG1: ↑ (ADL/IADL) IG2: ↑ (ADL/IADL) IG3: ↔ (ADL/IADL)	IG1: ↑ IG2: ↑ IG3: ↔	IG1: ↔ (CGR Burden) IG2: ↔ (CGR Burden) IG3: ↔ (CGR Burden)
Galantamine	Wilcock, 2000[210] Fair-Good	Dem	653	72	6	IG1: ↑ (CIBIC+[D]) IG2: ↑ (CIBIC+[D])	IG1: ↑ (ADAS-Cog), ↑ (ADAS-Cog [D]) IG2: ↑ (ADAS-Cog), ↑ (ADAS-Cog [D])	NR	IG1: ↔ (ADL/IADL) IG2: ↑ (ADL/IADL)	NR	NR
Galantamine	Wilkinson, 2001[211] Fair-Good	Dem	285	74	3	↔ (CIBIC+)	IG1: ↑ (ADAS-Cog) IG2: ↔ (ADAS-Cog) IG3: ↔ (ADAS-Cog)	NR	IG1: ↔ (ADL/IADL [D]) IG2: ↔ (ADL/IADL [D]) IG3: ↔ (ADL/IADL [D])	NR	NR
Rivastigmine	Agid, 1998[212] Fair-Good	Dem	402	69	3	NR	IG1: ↑ (MMSE) IG2: ↑ (MMSE)	IG1: ↔‡ (Attention), ↔‡ (Memory) IG2: ↔ (Attention), ↔‡ (Memory)	IG1: ↔ (ADL), ↔ (IADL) IG2: ↔ (ADL), ↔ (IADL)	NR	NR

Table 12. AChEIs and Memantine: Summary of Results, by Medication Type (KQ 4 and 5)

Medication	Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-specific Cognitive Function	Physical Function	Neuro Symptoms	Other
Rivastigmine	Ballard, 2008[213] Fair	Dem	710	73	6	↔ (CIBIC+), ↔ (GDS)	↑ (ADAS-Cog), ↑ (MMSE)	NR	↔ (ADL/IADL)	↔	NR
Rivastigmine	Corey-Bloom, 1998[214] Fair-Good	Dem	699	74	6	IG1: ↔ (CIBIC+[D]), ↑ (GDS) IG2: ↔ (CIBIC+[D]), ↔ (GDS)	IG1: ↑ (ADAS-Cog), ↔ (ADAS-Cog [D]), ↑ (MMSE) IG2: ↔ (ADAS-Cog), ↔ (MMSE)	NR		NR	NR
Rivastigmine	Feldman, 2007[215] Fair	Dem	678	71	6	IG1: ↑ (CIBIC+[D]), ↔ (GDS) IG2: ↔ (CIBIC+[D]), ↔ (GDS)	IG1: ↑ (ADAS-Cog), ↑ (ADAS-Cog [D]), ↔ (MMSE) IG2: ↑ (ADAS-Cog), ↔ (ADAS-Cog [D]), ↔ (MMSE)	NR	IG1: ↔ (ADL/IADL) IG2: ↔ (ADL/IADL)	NR	NR
Rivastigmine	McKeith, 2000[216] Fair-Good	Dem	120	74	5	NR	↔ (MMSE)	NR	NR	↑	NR
Rivastigmine	Mok, 2007[217] Fair	Dem	40	75	6	↔ (CDR-SB)	↔ (MMSE)	↔ (EF)	↔ (IADL)	↔	↔ (Anxiety)
Rivastigmine	Rosler, 1999[218] Fair-Good	Dem	725	72	6	IG1: ↑ (CIBIC+[D]), ↑ (GDS) IG2: ↔ (CIBIC+[D]), ↔ (GDS)	IG1: ↑ (ADAS-Cog), ↑ (ADAS-Cog [D]), ↑ (MMSE) IG2: ↔ (ADAS-Cog), ↔ (ADAS-Cog [D]), ↔ (MMSE)	NR		NR	NR
Rivastigmine	Winblad, 2007[219] Fair	Dem	1195	74	6	IG1: ↑ (CIBIC+[D]) IG2: ↔ (CIBIC+[D]) IG3: ↑ (CIBIC+[D])	IG1: ↑ (ADAS-Cog), ↑ (MMSE) IG2: ↑ (ADAS-Cog), ↑ (MMSE) IG3: ↑ (ADAS-Cog), ↑ (MMSE)	IG1: ↑ (Attention), ↔ (EF) IG2: ↑ (Attention), ↔ (EF) IG3: ↑ (Attention), ↔ (EF)	IG1: ↑ (ADL/IADL) IG2: ↑ (ADL/IADL) IG3: ↑ (ADL/IADL)	IG1: ↔ IG2: ↔ IG3: ↔	NR
Memantine	Bakchine, 2008[220] Good	Dem	470	74	6	↔ (CIBIC+)	↔ (ADAS-Cog)	NR	↔ (ADL/IADL)	↔	NR
Memantine	Choi, 2011*[221] Fair	Dem	172	75	4	↔ (CDR-SB)	↔ (ADAS-Cog), ↔ (MMSE)	↔ (EF)	↔ (ADL/IADL)	↔	NR

Table 12. AChEIs and Memantine: Summary of Results, by Medication Type (KQ 4 and 5)

Medication	Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-specific Cognitive Function	Physical Function	Neuro Symptoms	Other
Memantine	Dysken, 2014*[222] Good	Dem	613	79	48	NR	↔ (ADAS-Cog), ↔ (MMSE)		↔ (ADL/IADL)	↔	NR
Memantine	Ferris, 2007[223] Fair	MCI	60	67	3	NR	NR	↔ (Attention), ↔ (Memory)	NR	NR	NR
Memantine	Herrmann, 2013*[224] Fair	Dem	369	75	6	NR	↔ (SIB)	NR	NR	↔	↔ (Institutionalization)
Memantine	Orgogozo, 2002[225] Fair-Good	Dem	321	76	6	↔ (ADCS-CGIC), ↔ (CIBIC+[D]), ↔ (GBS)	↑ (ADAS-Cog), ↑ (MMSE)	NR	↔ (ADL), ↔ (IADL)	NR	NR
Memantine	Peskind, 2006[226] Fair-Good	Dem	403	78	6	↑ (CIBIC+)	↑ (ADAS-Cog)	NR	↔ (ADL/IADL)	↑	NR
Memantine	Peters, 2015*[227] Fair	Dem	226	72	12	↔ (CDR-SB)	↔ (ADAS-Cog)	NR	↔ (ADL/IADL)	↔	NR
Memantine	Porsteinsson, 2008[228] Good	Dem	433	75	6	↔ (CIBIC+)	↔ (ADAS-Cog), ↔ (MMSE)	NR	↔ (ADL/IADL)	↔	NR
Memantine	Saxton, 2012[229] Good	Dem	265	75	3	↔ (ADCS-CGIC[D])	NR	NR	NR	NR	NR
Memantine	Wilcock, 2002[230] Fair-Good	Dem	579	77	6	NR	↑ (ADAS-Cog)	NR	NR	NR	NR
Memantine	Wilkinson, 2012[231] Fair	Dem	278	74	12	NR	↑ (MMSE)	↔‡ (EF), ↑ (Language)	NR	↔	NR

NOTE: Arrows represent study-reported results.

Symbol Legend:
↑ = Statistically significant between-group difference in favor of intervention group
↔ = No statistically significant difference between groups or no clear between-group difference (not reported).

* New study
† Results are statistically significant for at least one timepoint
‡ Mixed results from multiple tests assessing same cognitive domain

Table 12. AChEIs and Memantine: Summary of Results, by Medication Type (KQ 4 and 5)

Abbreviations: ADL = Activities of Daily Living; ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive subscale; ADCS-CGIC = Alzheimer's Disease Cooperative Stud – Clinical Global Impression of Change scale; CIBIC+ = Clinician's Interview-Based Impression of Change with caregiver's input; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; CGI = Clinical Global Impression scale; CGR = caregiver; D = dichotomized; Dem = dementia; EF = executive functioning; FU = followup; GBS = Gottfries-Brane-Steen scale; GDS = Global Deterioration Scale; IADL = Instrumental Activities of Daily Living; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; mo. = months; NR = not reported; Pop cat = population category

Table 13. Other Medications and Supplements: Study Characteristics, by Agent (KQ 4 and 5)

Medication type	Medication	Author, year (Study name)	Quality	Country	N randomized	Population	Baseline MMSE, mean	Age, mean	Female, %
Antihypertensive	Discontinuation of antihypertensive	Moonen, 2015*[235] (DANTE)	Fair	NLD	385	MCI	26†	81	59
HMG-CoA reductase inhibitor	Atorvastatin	Feldman, 2010[236] (LEADe)	Fair	US	640	Dem	22.0	74	52
HMG-CoA reductase inhibitor	Simvastatin	Sano, 2011[237]	Fair	US	406	Dem	20.4	75	59
HMG-CoA reductase inhibitor	Simvastatin	Simons, 2002[238]	Fair	DEU	44	Dem	17.5	68	55
HMG-CoA reductase inhibitor	Atorvastatin	Sparks, 2005[239] (Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial)	Fair	US	63	Dem	20.8	78	36
NSAID	Naproxen	Aisen, 2003[240]	Good	US	229	Dem	20.9	74	53
NSAID	Indomethacin	de Jong, 2008[241]	Fair	NLD	51	Dem	19.6	72	65
NSAID	Ibuprofen	Pasqualetti, 2009[242]	Fair	ITA	132	Dem	20.0	74	63
NSAID	Celecoxib	Soininen, 2007[243]	Fair	US, GBR, AUS, BEL, FIN, FRA, DEU, NLD	425	Dem	19.7	74	55
Gonadal steroid	Estrogen	Henderson, 2000[245]	Fair	US	42	Dem	19.5	78	100
Gonadal steroid	Estrogen	Henderson, 2015*[244]	Good	US	42	Dem	20.3	76	100
Gonadal steroid	Testosterone	Lu, 2006[246]	Fair	US	18	Dem	22.0	70	0
Gonadal steroid	Estrogen	Mulnard, 2000[247]	Fair	US	120	Dem	20.7	75	100
Gonadal steroid	Estrogen plus progestin	Valen-Sendstad, 2010[248]	Fair	NOR	65	Dem	21.9	81	100
Gonadal steroid	Estrogen	Wang, 2000[249]	Fair	TWN	50	Dem	16.2	72	100
Dietary supplement	B vitamins (including folic acid)	Aisen, 2008[250]	Good	US	409	Dem	21.0	76	56
Dietary supplement	B vitamins (including folic acid)	Connelly, 2008[251]	Fair	GBR	57	Dem	24.0	76	71
Dietary supplement	B vitamins (including folic acid)	de Jager, 2012[252] (VITACOG)	Fair	GBR	271	MCI	NR	77	64
Dietary supplement	Vitamin E	Dysken, 2014*[222] (TEAM-AD VA)	Good	US	613	Dem	21.0	79	3

Table 13. Other Medications and Supplements: Study Characteristics, by Agent (KQ 4 and 5)

Medication type	Medication	Author, year (Study name)	Quality	Country	N randomized	Population	Baseline MMSE, mean	Age, mean	Female, %
Dietary supplement	Omega-3 fatty acids	Freund-Levi, 2006[253]	Fair	SWE	204	Dem	23.4	74	54
Dietary supplement	B vitamins (including folic acid)	Kwok, 2011[254]	Fair	HKG	140	Dem	16.6	78	64
Dietary supplement	Vitamin E	Petersen, 2005[194]	Fair	US, CAN	769	MCI	27.3	73	46
Dietary supplement	Omega-3 fatty acids	Phillips, 2015*[255]	Fair	GBR	76	MCI + Dem	NR	71	55
Dietary supplement	Omega-3 fatty acids	Quinn, 2010[256]	Fair	US	402	Dem	20.7	76	52
Dietary supplement	Vitamin E	Sano, 1997[257]	Good	US	169	Dem	12.3	73	66
Dietary supplement	Omega-3 and LA	Shinto, 2014*[258]	Fair	US	39	Dem	21.8	76	44
Dietary supplement	Omega-3 fatty acids - DHA	Sinn, 2012[259]	Fair	AUS	54	MCI	27.2	74	32
Dietary supplement	Multivitamin	Sun, 2007[260]	Fair	JPN	89	Dem	18.7	75	49
Dietary supplement	Omega-3 fatty acids	Yurko-Mauro, 2010[261]	Good	US	485	MCI	28.2	70	58

* New Study
† Median

Abbreviations: AUS = Australia; AUT = Austria; BEL = Belgium; CAN = Canada; CHE = Switzerland; CZE = Czech Republic; Dem = Dementia; DEU = Germany; DNK = Denmark; ESP = Spain; EST = Estonia; FIN = Finland; FRA = France; GBR = Great Britain/United Kingdom; GRC = Greece; GTM = Guatemala; HKG = Hong Kong; IRL = Ireland; ISR = Israel; ITA = Italy; JPN = Japan; KOR = Korea; LEADe = Lipitor's Effect in Alzheimer's; Dementia; LVA = Latvia; LTU = Lithuania; MCI = mild cognitive impairment; MEX = Mexico; MMSE = Mini-Mental State Examination; N = number of participants; NLD = Netherlands; NOR = Norway; NR = not reported; NZL = New Zealand; PER = Peru; POL = Poland; PRT = Portugal; ROU = Romania; RUS = Russia; SVK = Slovakia; SVN = Slovenia; SWE = Sweden; TWN = Taiwan; UKR = Ukraine; VEN = Venezuela; ZAF = South Africa

Table 14. Other Medications and Supplements: Intervention Characteristics, by Agent (KQ 4 and 5)

Author, year Quality	Country	Pop cat	Medication (total daily dose)	Duration, weeks	Intervention details	CG description
Moonen, 2015*[235] Fair	NLD	MCI	Discontinuation of antihypertensive treatment	16	During a 6-week period after randomization, the discontinuation of antihypertensive treatment according to an algorithm composed by the investigators; and until a maximum increase of 20 mm Hg in SBP was reached. Treatment was restarted when DBP was 120 mm	Usual care (continuation of anti-hypertensive treatment)
Feldman, 2010[236] Fair	US	Dem	Atorvastatin (80 mg)	72	80 mg qd and donepezil 10 mg qd	Placebo + donepezil (10 mg qd)
Sano, 2011[237] Fair	US	Dem	Simvastatin (40 mg)	78	Started at 20 mg qd of simvastatin for 6 weeks and increased to 40-mg qd for remainder of 18-month study.	Placebo
Simons, 2002[238] Fair	DEU	Dem	Simvastatin (80 mg)	26	40 mg qd for 4 weeks; 80 mg qd for rest of the study	Placebo
Sparks, 2005[239] Fair	US	Dem	Atorvastatin (80 mg)	52	80 mg qd (given two 40 mg tablets qd)	Placebo
Aisen, 2003[240] Good	US	Dem	Naproxen (440 mg)	52	220 mg bid	Placebo
de Jong, 2008[241] Fair	NLD	Dem	Indomethacin (100 mg)	52	50 mg bid and omeprazole 20 mg qd	Placebo bid + omeprazole (20 mg qd)
Pasqualetti, 2009[242] Fair	ITA	Dem	Ibuprofen (800 mg)	52	400 mg bid	Placebo + esomeprazole (20 mg) placebo
Soininen, 2007[243] Fair	US, GBR, AUS, BEL, FIN, FRA, DEU, NLD	Dem	Celecoxib (400 mg)	52	200 mg bid	Placebo
Henderson, 2000[245] Fair	US	Dem	Estrogen (1.25 mg)	16	Given daily as a single oral tablet of 1.25 mg for 16 weeks.	Placebo
Henderson, 2015*[244] Good	US	Dem	Estrogen (120 mg)	52	Started at two 60-mg tablets qd and continued through the end of the study.	Placebo

Table 14. Other Medications and Supplements: Intervention Characteristics, by Agent (KQ 4 and 5)

Author, year Quality	Country	Pop cat	Medication (total daily dose)	Duration, weeks	Intervention details	CG description
Lu, 2006[246] Fair	US	Dem	Testosterone (75 mg)	24	Applied three packets of 25 mg of T-gel on three different sites in the morning after showering or bathing for total dose of 75 mg.	Placebo
Mulnard, 2000[247] Fair	US	Dem	IG1: Estrogen (0.625 mg) IG2: Estrogen (1.24 mg)	52	IG1: Given one 0.625 mg and one identical placebo tablet qd for 12 months followed by a 3 month single-blind placebo washout period IG2: Given two 0.625 mg tablets qd for 12 months followed by a 3 month single-blind placebo washout period	Placebo
Valen-Sendstad, 2010[248] Fair	NOR	Dem	Estrogen plus progestin (1.5 mg)	52	Given 1 tablet containing 1 mg of estradiol and 0.5 mg norethisterone qd	Placebo
Wang, 2000[249] Fair	TWN	Dem	Estrogen (1.25 mg)	12	Given 1.25 mg of conjugated estrogen (Premarin); taken orally qd	Placebo
Aisen, 2008[250] Good	US	Dem	B vitamins (including folic acid) (31 mg)	78	31 mg qd for 78 weeks	Placebo
Connelly, 2008[251] Fair	GBR	Dem	B vitamins (including folic acid) (1 mg)	26	1 mg qd combined with AChEI of clinician's choice	Placebo and AChEI of clinician's choice
de Jager, 2012[252] Fair	GBR	MCI	B vitamins (including folic acid) (0.8 mg folic acid, 0.5 mg cyanocobalamin and 20 mg pyridoxine HCl)	104	NR	Placebo
Dysken, 2014*[222] Good	US	Dem	Vitamin E (2000 IU)	208	Alpha tocopherol at 1000 IU bid. Memantine placebo was titrated over 4 weeks.	Placebo
Freund-Levi, 2006[253] Fair	SWE	Dem	Omega-3 fatty acids (4 g)	26	Four 1g capsules qd	Isocaloric placebo oil (1 g corn oil, 0.6 g linoleic acid); vitamin E 4 mg added to each packet.
Kwok, 2011[254] Fair	HKG	Dem	B vitamins (including folic acid) (6 mg)	104		Placebo
Petersen, 2005[194] Fair	US, CAN	MCI	Vitamin E (2000 IU) and multivitamin	36	Started at 1000 IU qd, then increased to 2000 IU (1000 IU bid) after 6 weeks	Placebo + multivitamin containing 15 IU vitamin E

Table 14. Other Medications and Supplements: Intervention Characteristics, by Agent (KQ 4 and 5)

Author, year Quality	Country	Pop cat	Medication (total daily dose)	Duration, weeks	Intervention details	CG description
Phillips, 2015*[255] Fair	GBR	MCI + Dem	Omega-3 fatty acids (625 mg DHA + 600 mg EPA)	16	Started at a total of 625 mg of DHA and 600 mg of EPA	Placebo
Quinn, 2010[256] Fair	US	Dem	Omega-3 fatty acids (2 g)	78	1 g bid	Placebo
Sano, 1997 Good	US	Dem	Vitamin E (1.818 g)	104	0.909 g bid	Placebo
Shinto, 2014*[258] Fair	US	Dem	IG1: Omega-3 fatty acids (675 mg DHA + 975 mg EPA)	52	IG1: Fish oil concentrate containing a daily dose of 675 mg DHA + 975 mg EPA	Placebo
Sinn, 2012[259] Fair	AUS	MCI	IG1: Omega-3 fatty acids – DHA (1.95 g) IG2: Omega-3 fatty acids – EPA (1.83 g)	26	IG1: 1.95 g qd IG2: 1.83 g qd	Placebo (safflower oil containing 2.2 g linoleic acid qd)
Sun, 2007[260] Fair	JPN	Dem	Multivitamin (Mecobalamin [0.5 mg] + multivitamin supplement that contained folic acid, pyridoxine HCl, ferrous [60 mg], nicotinamide [10 mg], calcium carbonate [250 mg], riboflavin [2 mg], thiamine mononitrate [3 mg], calcium pantothenate [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])	26	To be taken after breakfast.	Placebo
Yurko-Mauro, 2010[261] Good	US	MCI	Omega-3 fatty acids (900 mg)	24	900 mg qd	Placebo

* New Study

Abbreviations: AChEI = acetyl-cholinesterase-inhibitor; AUS = Australia; BEL = Belgium; bid = twice a day; CAN = Canada; CG = control group; cm^2 = square centimeter; DBP = diastolic blood pressure; Dem = Dementia; DEU = Germany; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FIN = Finland; FRA = France; g = grams; GBR = Great Britain/United Kingdom; HKG = Hong Kong; IG = intervention group; ITA = Italy; IU = International Unit; JPN = Japan; KOR = Korea; LVA = Latvia; LTU = Lithuania; MCI = mild cognitive impairment; mcg = microgram; mg = milligram; MMSE = Mini-Mental State Examination; N = number of participants; NLD = Netherlands; NOR = Norway; Pop cat = population category; qd = once a day; SBP = systolic blood pressure; SWE = Sweden; tid = three times a day; TWN = Taiwan

Table 15. Other Medications and Supplements: Summary of Results, by Agent (KQ 4 and 5)

Medication type	Medication	Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-specific Cognitive Function	Physical Function	Neuro Symptoms	Other
Antihypertensive	Discontinuation of antihypertensive	Moonen, 2015*[235] Fair	MCI	385	81	4	NR	↔ (MMSE)	↔ (EF, Memory)	↔ (ADL/IADL)	↔ (Dep)	↔ (QOL)
HMG-CoA reductase inhibitor	Atorvastatin	Feldman, 2010[236] Fair	Dem	640	74	18	↔ (CIBIC+, CDR-SB)	↔ (ADAS-Cog 11, MMSE)	NR	↔ (ADL/IADL)	↔ (NPS)	NR
HMG-CoA reductase inhibitor	Simvastatin	Sano, 2011[237] Fair	Dem	406	75	18	NR	↔ (ADAS-Cog 11, MMSE)	NR	↔ (ADL/IADL)	↔ (NPS)	NR
HMG-CoA reductase inhibitor	Simvastatin	Simons, 2002[238] Fair	Dem	44	68	6	NR	↔ (ADAS-Cog 11), ↑ (MMSE)	NR	NR	NR	NR
HMG-CoA reductase inhibitor	Atorvastatin	Sparks, 2005[239] Fair	Dem	63	78	12	↔ (CIBIC+)	↔ (ADAS-Cog 11, MMSE)	NR	↔ (ADL/IADL)	↑ (Dep)	NR
NSAID	Naproxen	Aisen, 2003[240] Good	Dem	229	74	12	↔ (CDR-SB)	↔ (ADAS-Cog 11)	NR	↔ (ADL/IADL)	↔ (NPS)	↔ (QOL)
NSAID	Indomethacin	de Jong, 2008[241] Fair	Dem	51	72	12	↔ (CIBIC+)	↔ (ADAS-Cog 11, MMSE)	NR	NR	↔ (NPS)	↔ (CGR Burden)
NSAID	Ibuprofen	Pasqualetti, 2009[242] Fair	Dem	132	74	12	↔ (CDR-SB, CIBIC+)	↔ (ADAS-Cog 11, MMSE)	NR	↔ (ADL, IADL)	↔ (Dep, NPS)	↔ (CGR Anxiety, Depression, Burden) ↔ (Institutionalization)
NSAID	Celecoxib	Soininen, 2007[243] Fair	Dem	425	74	6	↔ (CIBIC+)	↔ (ADAS-Cog 11, ADAS-Cog 11 [D], MMSE)	NR	NR	↔ (NPS)	↔ (QOL)
Gonadal steroid	Estrogen	Henderson, 2000[245] Fair	Dem	42	78	4	↔ (CIBIC+, CIBIC+ [D])	↔ (ADAS-Cog 11, ADAS-Cog 11 [D])	↔ (Attention), ↑ (EF), ↔* (Memory)	↔ (IADL)	↔ (Dep)	NR

Table 15. Other Medications and Supplements: Summary of Results, by Agent (KQ 4 and 5)

Medication type	Medication	Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-specific Cognitive Function	Physical Function	Neuro Symptoms	Other
Gonadal steroid	Estrogen	Henderson, 2015*[244] Good	Dem	42	76	12	↔ (CDR, CDR-SB)	↔ (ADAS-Cog 11, MMSE)	↔ (Attention, EF, Language), ↔* (Memory)	↔ (ADL/IADL)	↔ (NPS)	↔ (CGR Burden)
Gonadal steroid	Testosterone	Lu, 2006[246] Fair	Dem	18	70	6	↔ (CIBIC+)	↔ (ADAS-Cog 11)	↔ (EF, Memory)	NR	↔ (Dep, NPS)	↔ (QOL)
Gonadal steroid	Estrogen	Mulnard, 2000[247] Fair	Dem	120	75	12	IG1: ↓ (CDR), ↔ (CIBIC+, CIBIC+ [D]) IG1: ↓ (CDR), ↔ (CIBIC+, CIBIC+ [D])	IG1: ↔ (ADAS-Cog 11, MMSE) IG2: ↔ (ADAS-Cog 11, MMSE)	IG1: ↔ (Attention, Language, Memory) IG2: ↔ (Attention, Language, Memory)	↔ (ADL)	↔ (Dep)	NR
Gonadal steroid	Estrogen plus progestin	Valen-Sendstad, 2010[248] Fair	Dem	65	81	12	IG1: ↔ (GDS)	↔ (MMSE)	↔ (Attention, Language, Memory)	↔ (ADL)	↔ (Dep)	NR
Gonadal steroid	Estrogen	Wang, 2000[249] Fair	Dem	50	72	3	↔ (CDR, CIBIC+)	↔ (MMSE)	NR	NR	↔ (Anx, Dep, NPS)	NR
Dietary supplement	B vitamins (including folic acid)	Aisen, 2008[250] Good	Dem	409	76	18	↔ (CDR-SB)	↔ (ADAS-Cog 11, MMSE)	NR	↔ (ADL/IADL)	↔ (NPS)	↔ (QOL)
Dietary supplement	B vitamins (including folic acid)	Connelly, 2008[251] Fair	Dem	57	76	6	↑ (Unspecified [D])	↔ (MMSE)	↔ (Attention)	↑ (IADL)	NR	NR
Dietary supplement	B vitamins (including folic acid)	de Jager, 2012[252] Fair	MCI	271	77	24	NR	NR	↑ (EF) ↔ (Language, Memory)	NR	↔ (Dep)	NR
Dietary supplement	Vitamin E	Dysken, 2014*[222] Good	Dem	613	79	48	NR	↔ (ADAS-Cog 11, MMSE)	NR	↑ (ADL/IADL)	↔ (NPS)	NR

Table 15. Other Medications and Supplements: Summary of Results, by Agent (KQ 4 and 5)

Medication type	Medication	Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-specific Cognitive Function	Physical Function	Neuro Symptoms	Other
Dietary supplement	Omega-3 fatty acids	Freund-Levi, 2006[253] Fair	Dem	204	74	6	↔ (CDR, CDR-SB)	↔ (ADAS-Cog 13, MMSE)	NR	↔ (ADL/IADL)	↔ (Dep, NPS)	NR
Dietary supplement	B vitamins (including folic acid)	Kwok, 2011[254] Fair	Dem	140	78	24	NR	↔ (MDRS, MMSE)	↔ (Attention, EF, Memory)	NR	↔ (Dep, NPS)	NR
Dietary supplement	Vitamin E	Petersen, 2005[194] Fair	MCI	769	73	36	↔ (CDR-SB, ↔ GDS)	↔ (ADAS-Cog 11, ADAS-Cog 13, MMSE)	↔* (EF, Language) ↔ (Memory)	↔ (IADL)	NR	↔ (Dementia Incidence)
Dietary supplement	Omega-3 fatty acids	Phillips, 2015*[255] Fair	MCI + Dem	76	71	4	NR	NR	↔ (Attention, EF, Language, Memory)	↔ (ADL/IADL)	↔ (Dep)	NR
Dietary supplement	Omega-3 fatty acids	Quinn, 2010[256] Fair	Dem	402	76	18	↔ (CDR-SB)	↔ (ADAS-Cog 11, MMSE)	NR	↔ (ADL/IADL)	↔ (NPS)	NR
Dietary supplement	Vitamin E	Sano, 1997[257] Good	Dem	169	73	24	↔ (CDR [D])	↔ (ADAS-Cog 11, MMSE)	NR	↑ (ADL [D])	NR	↔ (Institutionalization)
Dietary supplement	Omega-3 and LA	Shinto, 2014*[258] Fair	Dem	39	76	12	NR	IG1: ↔ (ADAS-Cog 11), ↔ (MMSE) IG2: ↔ (ADAS-Cog 11), ↑ (MMSE)	NR	IG1: ↔ (ADL), ↑ (IADL) IG2: ↔ (ADL), ↑ (IADL)	NR	NR
Dietary supplement	Omega-3 fatty acids - DHA	Sinn, 2012[259] Fair	MCI	54	74	6	NR	NR	IG1: ↔ (Attention, Language), ↔* (EF) IG2: ↔ (Attention, EF, Language)	NR	IG1: ↑ (Dep) IG2: ↑ (Dep)	↔ (QOL)
Dietary supplement	Multivitamin	Sun, 2007[260] Fair	Dem	89	75	6	NR	↔ (ADAS-Cog 11, MMSE)	↔* (Memory)	↔ (ADL, IADL)	NR	NR

Table 15. Other Medications and Supplements: Summary of Results, by Agent (KQ 4 and 5)

Medication type	Medication	Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-specific Cognitive Function	Physical Function	Neuro Symptoms	Other
Dietary supplement	Omega-3 fatty acids	Yurko-Mauro, 2010[261] Good	MCI	485	70	6	NR	↔ (MMSE)	↑ (EF), ↔* (Memory)	↔ (ADL)	↔ (Dep)	NR

NOTE: Arrows represent study-reported results.

Symbol Legend:
↑ = Statistically significant between-group difference in favor of intervention group
↔ = No statistically significant difference between groups or no clear between-group difference (not reported).
↓= Statistically significant between-group difference in favor of control group

Abbreviations: ADAS-Cog 11 = Alzheimer's Disease Assessment Scale-cognitive subscale; 11-item; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-cognitive subscale; 13-item; ADL = Activities of Daily Living; Anx = anxiety; CDR = Clinical Dementia Rating Scale; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; CIBIC+ = Clinician's Interview-Based Impression of Change with caregiver's input; D = dichotomized; Dem = dementia; Dep = depression; DHA = docosahexaenoic acid; EF = executive functioning; FU = followup; GDS = global deterioration scale; HMG-CoA = β-Hydroxy β-methylglutaryl-CoA; IADL = Instrumental Activities of Daily Living; IG = intervention group; LA = linoleic acid; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NPS = Composite neuropsychiatric symptoms; NR = not reported; N rand = number of participants randomized; NSAID = Nonsteroidal Anti-inflammatory Drug; Pop cat = population category; QOL = quality of life

Table 16. Patient-Level Nonpharmacologic Interventions: Study Characteristics, by Intervention (KQ 4 and 5)

Author, year (Study name)	Quality	Country	N rand	Population	Baseline MMSE, mean	Age, mean	Female, %	AChEI or memantine use, %
Cognitive Stimulation, Training, and Rehabilitation								
Amieva, 2016*[275] (ETNA3)	Good	FRA	481	Dem	21.5	79	58	88
Belleville, 2018[289] (MEMO+)	Fair	CAN	145	MCI	NR	72	55	NR
Bergamaschi, 2013*[280]	Fair	ITA	32	Dem	21.1	78	NR	100
Buschert, 2011[269]	Fair	DEU	39	MCI + Dem	26.4	73	51	41
Cahn-Weiner, 2003[267]	Fair	US	34	Dem	24.7	77	59	100
Cavallo, 2016*[284]	Good	ITA	80	Dem	22.9	76	64	92
Chapman, 2004[266]	Fair	US	54	Dem	20.9	76	54	NR
Cove, 2014*[277]	Fair	GBR	68	Dem	22.6	77	47	57
Fiatarone Singh, 2014*[278] (SMART[a])	Fair	AUS	78	MCI	27.0	70	68	NR
Greenaway, 2012[271]	Fair	US	40	MCI	26.8	72	61	NR
Herrera, 2012*[281]	Fair	FRA	22	MCI	27.3	77	50	NR
Hyer, 2016*[285]	Fair	US	77	MCI	26	75	53	0
Jelcic, 2012*[282]	Fair	ITA	40	Dem	24.7	82	82	0
Jeong, 2016*[274]	Fair	KOR	293	MCI	25.7	70	63	34
Kallio, 2018[288] (FINCOG)	Fair	FIN	147	Dem	20.5	83	72	83
Kinsella, 2009[264]	Fair	AUS	54	MCI	26.0	77	57	NR
Kurz, 2012[272] (CORDIAL)	Fair	DEU	201	Dem	25.1	74	44	NR
Nousia, 2018[286]	Fair	GRC	50	Dem	NR	76	72	NR
Olazaran, 2004[265]	Fair	ESP	84	MCI + Dem	NR	74	60	100
Orrell, 2014*[279]	Good	GBR	236	Dem	17.8	83	64	32
Orrell, 2017*[273]	Good	GBR	356	Dem	21.2	78	46	76
Pantoni, 2017 (RehAtt)[287]	Fair	ITA	46	MCI	26.4	75	35	0
Quayhagen, 1995[270]	Fair	US	63	Dem	NR	74	35	NR
Rapp, 2002[268]	Fair	US	19	MCI	27.6	74	58	0
Troyer, 2008[262]	Fair	CAN	54	MCI	27.9	75	54	NR
Tsantali, 2017*[283]	Fair	GRC	63	Dem	22.9	74	NR	100
Tsolaki, 2011[263]	Fair	GRC	196	MCI	27.9	68	72	0
Vidovich, 2015*[276] (PACE)	Good	AUS	160	MCI	NR	75	54	NR
Exercise Interventions								
Baker, 2010[296]	Fair	US	33	MCI	27.4	70	52	NR
Blumenthal, 2018[307] (ENLIGHTEN)	Fair	US	160	MCI	NR	65	66	NR
Dawson, 2016*[305]	Fair	US	26	Dem	20.8	74	56	NR
Doi, 2017*[304]	Good	JPN	134	MCI	25.9	76	48	0

Table 16. Patient-Level Nonpharmacologic Interventions: Study Characteristics, by Intervention (KQ 4 and 5)

Author, year (Study name)	Quality	Country	N rand	Population	Baseline MMSE, mean	Age, mean	Female, %	AChEI or memantine use, %
Ho, 2018[308]	Fair	HKG	204	MCI + Dem	NR	79	82	NR
Hoffmann, 2016*[302] (ADEX)	Good	DNK	200	Dem	23.9	70	56	96
Holthoff, 2015*[303]	Fair	DEU	30	Dem	22.0	72	50	100
Hong, 2017*[300]	Fair	KOR	25	MCI	NR	77	64	NR
Karssemeijer, 2019[310]	Fair	NLD	115	Dem	22.4	80	46	21
Lam, 2011[293]	Fair	HKG	389	MCI	24.5	78	76	NR
Lamb, 2018[306] (DAPA)	Good	GBR	494	Dem	21.9	77	61	55
Lautenschlager, 2008[292] (FAB)	Good	AUS	170	MCI	NR	68	51	NR
Lazarou, 2017*[299]	Fair	GRC	154	MCI	27.2	67	78	NR
Liu-Ambrose, 2016*[291] (PROMOTE)	Fair	CAN	70	Dem	26.4	74	51	NR
Morris, 2017*[301] (ADEPT)	Good	US	76	MCI + Dem	25.4	73	51	NR
Pitkälä, 2013*[290] (FINALEX)	Good	FIN	210	Dem	18.0	78	39	96
Schwenk, 2010[294]	Fair	DEU	61	Dem	21.4	82	64	NR
Siu, 2018[309]	Fair	HKG	160	MCI	25.0	NR	74	0
Suzuki, 2012[297]	Fair	JPN	50	MCI	26.7	76	46	NR
Venturelli, 2010[295]	Fair	ITA	30	MCI + Dem	NR	84	NR	NR
Vreugdenhil, 2012[298]	Fair	AUS	40	Dem	22.0	74	60	63
Multicomponent and Other Interventions								
Bae, 2019[320]	Fair	JPN	83	MCI	26.9	76	48	NR
Bellantonio, 2008[311]	Fair	US	100	Dem	14.8	82	63	NR
Belleville, 2018[289] (MEMO+)	Fair	CAN	145	MCI	NR	72	55	NR
Blumenthal, 2018[307] (ENLIGHTEN)	Fair	US	160	MCI	NR	65	66	NR
Burgener, 2008[312]	Fair	US	43	Dem	24.0	77	46	NR
Jha, 2013*[316]	Fair	GBR	48	MCI + Dem	22.0	79	67	NR
Karssemeijer, 2019[310]	Fair	NLD	115	Dem	22.4	80	46	21
Marshall, 2015*[315] (Living Well with Dementia)	Fair	GBR	58	Dem	23.0	76	57	81
Quinn, 2016*[314] (SMART[b])	Good	GBR	24	Dem	23.6	76	25	NR
Richard, 2009[317]	Fair	NLD	123	Dem	22.3	76	57	32
Rovner, 2018[318]	Good	US	221	MCI	25.7	76	79	0
Shimada, 2017[321]	Fair	JPN	308	MCI	26.7	72	50	0
Straubmeier, 2017[322] (DeTMAKS)	Fair	DEU	453	MCI + Dem	19.6	81	61	28

Table 16. Patient-Level Nonpharmacologic Interventions: Study Characteristics, by Intervention (KQ 4 and 5)

Author, year (Study name)	Quality	Country	N rand	Population	Baseline MMSE, mean	Age, mean	Female, %	AChEI or memantine use, %
Train the Brain Consortium, 2017[319] (TTB)	Fair	ITA	113	MCI	25.6	74	49	NR
Wolfs, 2008[313]	Fair	NLD	230	MCI + Dem	20.0	78	64	14

* New study

Abbreviations: AChEI = acetyl-cholinesterase-inhibitor; ADEPT = Alzheimer's Disease Exercise Program Trial; ADEX = Preserving Cognition, Quality of Life, Physical Health and Functional Ability in Alzheimer's Disease: The Effect of Physical Exercise; AUS = Australia; CORDIAL= Cognitive Rehabilitation and Cognitive-behavioral Treatment for Early Dementia in Alzheimer Disease; DAPA = Dementia and Physical Activity; DeTMAKS = Dementia Day Care Motor, Activities of daily living, Cognitive, Social; DEU = Germany; ENLIGHTEN = Exercise and NutritionaL Interventions for coGnitive and Cardiovascular HealTh Enhancement; ESP = Spain; FAB = Fitness for the Aging Brain; FIN = Finland; FINALEX = Finnish Alzheimer Disease Exercise Trial; FINCOG = Finnish Cognitive Training Trial; MEMO = Methode d'Entrainement pour Memoire Optimale; MMSE = Mini-Mental State Examination; FRA = France; GBR = Great Britain/United Kingdom; GRC = Greece; HKG = Hong Kong; ITA = Italy; JPN = Japan; KOR = Korea; MCI = mild cognitive impairment; N = number of participants; NLD = Netherlands; NR = not reported; PACE = Promoting Healthy Ageing with Cognitive Exercise; PROMOTE = Promotion of the Mind Through Exercise; RehAtt = Rehabilitation of Attention; SMART(a) = Study of Mental and Resistance Training; SMART(b) = Self-management group intervention for people with early-stage dementia; TTB = Train the Brain

Table 17. Patient-Level Nonpharmacologic Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Pop cat	Intervention type	Brief intervention group description	Duration, months	Brief control group description
Cognitive Stimulation, Training, and Rehabilitation						
Amieva, 2016*[275] Good	FRA	Dem	IG1: Cognitive training IG2: Cognitive rehabilitation	IG1: Group-based cognitive training for 1 d/wk, 90 min/d for first 3 months followed by maintenance sessions once every 6 months for the next 21 months plus separate caregiver support group sessions. IG2: Individualized cognitive rehabilitation for 1 d/wk, 90 min/d over the first 3 months followed by maintenance sessions once every 6 months for the next 21 months plus ongoing caregiver support through telephone calls.	24	UC: Patients received usual care while caregivers were offered the same support group sessions as cognitive training intervention arm.
Belleville, 2018[289] Fair	CAN	MCI	IG1: Cognitive training IG2: Other	IG1: Group-based cognitive training for 1 d/wk, 120 min/d for 2 months followed by one intensive booster session delivered three months later. IG2: Group-based cognitive behavioral therapy for 1 d/wk, 120 min/d for 2 months followed by one intensive booster session delivered three months later.	2.2	WL: Offered cognitive training intervention after study ended.
Bergamaschi, 2013*[280] Fair	ITA	Dem	Cognitive training	Group-based cognitive training over 5 one-month cycles over 1 year. Each cycle was 5 d/wk (20 sessions total) for 90 min/d.	12	Sham: Group-based cognitive activities during multiple, daily sessions (total # of sessions NR).
Buschert, 2011[269] Fair	DEU	MCI + Dem	Cognitive stimulation and training	Group-based cognitive stimulation therapy and cognitive training over 20 sessions for 90 min/d over 6 months; stimulation and training activities were conducted and tailored separately for MCI and AD patients.	6	Sham: Paper-pencil cognitive exercises for self-study plus 6 monthly group-based sessions to review self-study exercises.
Cahn-Weiner, 2003[267] Fair	US	Dem	Cognitive training	Group-based cognitive training focused specifically on memory training for 1 d/wk over 6 weeks.	2	BI: Group-based general education and support regarding aging and dementia 1 d/wk for 6 weeks.

Table 17. Patient-Level Nonpharmacologic Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Pop cat	Intervention type	Brief intervention group description	Duration, months	Brief control group description
Cavallo, 2016*[284] Good	ITA	Dem	Cognitive training	Computerized, individual-based cognitive training ("Brainer1") with neuropsychologist for 3 d/wk, 30 min/d over 3 months.	3	Sham: Computerized cognitive training sessions following same schedule as intervention (3 d/wk, 30 min/d) with neuropsychologist, but with general Internet browsing, reading, and games and no structured cognitive training.
Chapman, 2004[266] Fair	US	Dem	Cognitive stimulation	Group-based cognitive stimulation therapy for 1 d/wk, 90 min/d over 2 months.	2	WL: Caregivers encouraged to attend education classes that were also offered to intervention group and offered stimulation program at end of study.
Cove, 2014*[277] Fair	GBR	Dem	IG1: Cognitive stimulation IG2: Cognitive stimulation	IG1: Group-based cognitive stimulation therapy for 1 d/wk, 45 min/d over 3 months plus caregiver training on cognitive stimulation during two 60-180 min group sessions. IG2: Group-based cognitive stimulation therapy for 1 d/wk, 45 min/d over 3 months.	3	WL: Offered intervention after completion of study.
Greenaway, 2012[271] Fair	US	MCI	Cognitive training	Dyad training on the use of a calendar and note-taking system ("Memory Support System") to teach adaptation to memory loss (versus memory improvement) during 12 sessions for 60 min/session over 1.5 months.	1.5	None: Given same calendar as intervention group and encouraged to use it on their own without further instruction.
Herrera, 2012*[281] Fair	FRA	MCI	Cognitive training	Computerized, individual-based cognitive training focused on memory and attention with neuropsychologist supervision for 2 d/wk, 60 min/d over 3 months.	3	Sham: Paper-pencil general cognitive activities following same schedule as intervention (2 d/wk, 60 min/d) with neuropsychologist
Hyer, 2016*[285] Fair	US	MCI	Cognitive training	Computerized, individual-based cognitive training ("Cogmed QM©") focused on working memory for 25 sessions, 40 min/session over 1-2 months.	2	Sham: Computerized cognitive training sessions following same schedule as intervention (25 sessions, 40 min/session) and same general activities as Cogmed but without adaptivity based on individual's performance.

Table 17. Patient-Level Nonpharmacologic Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Pop cat	Intervention type	Brief intervention group description	Duration, months	Brief control group description
Jelcic, 2012*[282] Fair	ITA	Dem	Cognitive stimulation	Group-based cognitive stimulation therapy (Lexical-Semantic Stimulation) for 2 d/wk, 60 min/d over 3 months.	3	Sham: Group-based unstructured cognitive stimulation following same schedule as intervention (2 d/wk, 60 min/d) including creative work, reading plus discussion, and activities for improving verbal skills.
Jeong, 2016*[274] Fair	KOR	MCI	IG1: Cognitive training IG2: Cognitive training	IG1: Group-based cognitive training for 2 d/wk, 90 min/d over 3 months. IG2: Home-based cognitive training using print-based materials for 5 d/wk for 3 months with visits to the clinic every week in the 1st month and every other week in the 2nd and 3rd months to check and discuss homework materials.	3	WL: Offered cognitive training after study ended.
Kallio, 2018[288] Fair	FIN	Dem	Cognitive training	Group-based cognitive training focused to stimulate sub-skills of executive function for 2 d/wk, 45 min/d for 12 weeks.	3	UC: Usual care with routine treatment at a day care center twice a week for 6 hrs/d.
Kinsella, 2009[264] Fair	AUS	MCI	Cognitive rehabilitation	Individualized cognitive rehabilitation focused on memory difficulties for 1 d/wk, 90 min/d over 5 weeks.	1.25	WL: Offered intervention after study ended.
Kurz, 2012[272] Fair	DEU	Dem	Cognitive rehabilitation	Individualized cognitive rehabilitation 1 d/wk, 60 min/d over 3 months.	3	UC: Site-specific standard medical management including occupational therapy, physiotherapy, carer counseling, carer support groups, or medication alone.
Nousia, 2018[286] Fair	GRC	Dem	Cognitive training	Individual cognitive training sessions for 2 d/wk, 60-min/d.	3	UC: Standard care.
Olazaran, 2004[265] Fair	ESP	MCI + Dem	Cognitive stimulation	Group-based cognitive stimulation therapy 2 d/wk, 210 min/d over 1 year plus telephone help-line for caregivers.	12	MI: Psychosocial support (not described) plus telephone help-line for caregivers.
Orrell, 2014*[279] Good	GBR	Dem	Cognitive stimulation	Group-based maintenance cognitive stimulation therapy for 1 d/wk, 45 min/d for 6 months following a 7 week cognitive stimulation program.	6	UC: Site-specific usual care following a 7 week cognitive stimulation program.

Table 17. Patient-Level Nonpharmacologic Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Pop cat	Intervention type	Brief intervention group description	Duration, months	Brief control group description
Orrell, 2017*[273] Good	GBR	Dem	Cognitive stimulation	Home-based caregiver-led cognitive stimulation therapy for 3 d/wk, 30 min/d over 6 months.	6	UC: Site-specific usual care excluding cognitive stimulation, but including group-based activities such as gardening and support groups.
Pantoni, 2017[287] Fair	ITA	MCI	Cognitive training	Individual cognitive training 1 d/wk, 120-min/d over 5 months.	5	UC: Instructed to continue usual activities and provided with standard care (medication and clinic consultations).
Quayhagen, 1995[270] Fair	US	Dem	Cognitive stimulation	Home-based caregiver-led cognitive stimulation therapy for 1 d/wk, 60 min/d over 3 months.	3	WL: Offered training on cognitive stimulation after study ended.
Rapp, 2002[268] Fair	US	MCI	Cognitive training	Group-based cognitive training focused on memory enhancement for 1 d/wk, 120 min/d over 6 weeks.	1.5	None: Given copies of intervention print materials after study ended.
Troyer, 2008[262] Fair	CAN	MCI	Cognitive stimulation	Group-based cognitive stimulation therapy focused on memory enhancement for 10 sessions, 120 min/session over 6 months.	6	WL: Offered intervention after study ended.
Tsantali, 2017*[283] Fair	GRC	Dem	IG1: Cognitive training IG2: Cognitive stimulation	IG1: Individual-based cognitive training focused on memory enhancement for 3 d/wk, 90 min/d for 4 months. IG2: Individual-based non-specific cognitive stimulation activities for 3 d/wk, 90 min/d for 4 months.	4	WL: Offered intervention after study ended.
Tsolaki, 2011[263] Fair	GRC	MCI	Cognitive stimulation and training	Group-based cognitive training, cognitive stimulation therapy, and cognitive-behavioral therapy for 3 d/wk, 90 min/d over 6 months.	6	WL: Offered intervention after study ended.
Vidovich, 2015[276] Good	AUS	MCI	Cognitive rehabilitation, training, stimulation	Group-based cognitive training, stimulation, and rehabilitation for 2 d/wk, 90 min/d for 5 weeks.	1	MI: Group-based general education on healthy aging for 2 d/wk, 90 min/day over 5 weeks.
Exercise Interventions						
Baker, 2010[296] Fair	US	MCI	Exercise	Supervised individual-based aerobic exercise for 4 d/wk, 45-60 min/d over 6 months.	6	MI: Prescribed stretching and balance exercises.
Blumenthal, 2018[307] Fair	US	MCI	IG1: Exercise and diet counseling IG2: Exercise	IG1: Supervised exercise for 3 d/wk, 45-min/d over three months; unsupervised home exercise sessions 3 d/wk, 45min/d over subsequent three months; and dietary counseling for 1 d/wk, 30-	6	AC: Instructed to maintain their normal activities, and educational calls on CVD health-related topics 1 d/wk, 30-min/d for three months and

Table 17. Patient-Level Nonpharmacologic Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Pop cat	Intervention type	Brief intervention group description	Duration, months	Brief control group description
			IG3: Diet counseling	min/d for three months and 2 d/month, 30-min/d over subsequent three months IG2: Supervised exercise for 3 d/wk, 45-min/d over three months; unsupervised home exercise sessions 3 d/wk, 45min/d over subsequent three months IG3: Dietary counseling for 1 d/wk, 30-min/d for three months and 2 d/month, 30-min/d over subsequent three months.		2 d/month for subsequent three months.
Dawson, 2016*[305] Fair	US	Dem	Exercise	Supervised individual, home-based functional strength and balance exercises for 2 d/wk over 3 months.	3	WL: Maintain normal activities.
Doi, 2017*[304] Good	JPN	MCI	Exercise	Supervised group-based ballroom dancing for 1 d/wk, 60 min/d over 10 months.	10	AC: Three 90-min health education classes on general older adult health topics.
Ho, 2018[308] Fair	HKG	MCI + Dem	Exercise	IG1: Dance-movement group-based intervention for 2 d/wk, 60-min/d over three months. IG2: Supervised group-based exercise intervention for 2 d/wk, 60-min/d over three months.	IG1: 3 IG2: 12	WL: Usual care plus wait list intervention.
Hoffmann, 2016*[302] Good	DNK	Dem	Exercise	Supervised group-based aerobic exercise for 3 d/wk, 60 min/d over 4 months.	4	UC: Treatment as usual with access to memory clinic staff as needed.
Holthoff, 2015*[303] Fair	DEU	Dem	Exercise	Self-guided individual, home-based lower body exercises on computer-controlled movement trainer for 3 d/wk, 30 min/d over 3 months.	3	BI: Monthly clinic visits and general advice on changing inactive habits and increasing physical activity.
Hong, 2017*[300] Fair	KOR	MCI	Exercise	Supervised group-based M42resistance exercises using elastic band for 2 d/wk, 60 min/d over 3 months.	3	None: Maintain normal activities.
Karssemeijer, 2019[310] Fair	NLD	Dem	IG1: Multicomponent IG2: Exercise	IG1: Supervised combined cognitive-aerobic exercise sessions for 3 d/wk, 30-50 min/d for 3 months. IG2: Supervised aerobic exercise sessions for 3 d/wk, 30-50 min/d for 3 months.	3	Sham: Relaxation and stretching exercises for 3 d/week, 30-min/d over 3 months.

Table 17. Patient-Level Nonpharmacologic Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Pop cat	Intervention type	Brief intervention group description	Duration, months	Brief control group description
Lam, 2011[293] Fair	HKG	MCI	Exercise	Supervised group-based and self-guided Tai Chi for minimum of 1 d/wk, 30 min/d over 2-3 months.	3	MI: Supervised stretching and toning exercises at same intensity as intervention group (1 d/wk for 30 min/day).
Lamb, 2018[306] Good	GBR	Dem	Exercise	Dance-movement group-based intervention for 2 d/wk, 60-min/d over three months.	12	WL: Usual care plus wait list intervention.
Lautenschlager, 2008[292] Good	AUS	MCI	Exercise	Self-guided individually-tailored aerobic exercise for 3 d/wk, 50 min/d (minimum of 150 min/wk) + workbook over 6 months.	6	AC: Educational material about general health topics, excluding physical activity.
Lazarou, 2017*[299] Fair	GRC	MCI	Exercise	Supervised group-based ballroom dancing for 2 d/wk, 60 min/d over 10 months.	10	None: Maintain normal activities.
Liu-Ambrose, 2016*[291] Fair	CAN	Dem	Exercise	Supervised group-based aerobic exercise for 3 d/wk, 60 min/d over 6 months.	6	UC: Usual care plus monthly educational materials about vascular cognitive impairment and healthy diet.
Morris, 2017*[301] Good	US	MCI + Dem	Exercise	Supervised individual-based aerobic exercise for 3-5 d/wk, 30-50 min/d (150 min/wk) over 6 months.	6	MI: Supervised non-aerobic exercises (core strengthening, resistance bands, modified tai chi, modified yoga) at same intensity as intervention group (3-5 d/wk for 30-50 min/d).
Pitkälä, 2013*[290] Good	FIN	Dem	IG1: Exercise IG2: Exercise	IG1: Supervised group-based exercise focused on endurance, balance, strength training, and executive functioning for 2 d/wk, 60 min/d over 1 year. IG2: Supervised home-based individually-tailored functional mobility exercises for 2 d/wk, 60 min/d over 1 year.	12	UC: Usual care plus general advice on nutrition and exercise.
Schwenk, 2010[294] Fair	DEU	Dem	Exercise	Supervised group-based resistance-balance and functional-balance training, including specific dual-task training for concurrent motor or cognitive tasks for 2 d/wk, 120 min/d over 3 months.	3	MI: Supervised group-based motor placebo training including flexibility exercises, calisthenics, and ball games while seated for 2 d/wk, 60 min/d over 1 year.

Table 17. Patient-Level Nonpharmacologic Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Pop cat	Intervention type	Brief intervention group description	Duration, months	Brief control group description
Siu, 2018[309] Fair	HKG	MCI	Exercise	Supervised group-based Tai Chi for 2 d/wk, 60-min/d over 4 months and telephone followup for emotional support and reinforcement of intervention.	4	UC: Usual care and advised to attend recreational activities provided by their elderly centers and to continue their daily activities.
Suzuki, 2012[297] Fair	JPN	MCI	Exercise	Supervised group-based exercise including aerobic exercise, strength training, balance retraining, and dual-task training for 2 d/wk, 90 min/d over 1 year.	12	AC: Three general health education classes.
Venturelli, 2010[295] Fair	ITA	MCI + Dem	Exercise	Supervised group-based resistance training for 3 d/wk, 45 min/d over 3 months plus usual physical therapy.	3	UC: Usual physical therapy including electrostimulation, massage, and passive leg movement on bed as well as bingo, music therapy, and patchwork.
Vreugdenhil, 2012[298] Fair	AUS	Dem	Exercise	Self- and caregiver-guided home-based exercise including aerobic exercise, strength and balance training recommended to be performed daily over 4 months.	4	WL: Usual care plus wait list intervention.
Multicomponent and Other Interventions						
Bae, 2019[320] Fair	JPN	MCI	Multicomponent	Multicomponent group-based intervention with supervised exercise and cognitive and social activities 2d/wk, 90-min/d.	6	AC: Two 90-min health education classes about oral care and nutrition.
Bellantonio, 2008[311] Fair	US	Dem	Multidisciplinary assessment	Four multidisciplinary assessments by geriatrician, physical therapist, dietitian, and medical social worker and associated care recommendations provided over 9 months to new dementia-specific assisted living patients.	9	UC: Medical evaluation by primary care physician within 7 days of admission.
Belleville, 2018[289] Fair	CAN	MCI	IG1: Cognitive training IG2: Other	IG1: Group-based cognitive training for 1 d/wk, 120 min/d for 2 months followed by one intensive booster session delivered three months later. IG2: Group-based cognitive behavioral therapy for 1 d/wk, 120 min/d for 2 months followed by one intensive booster session delivered three months later.	2.2	WL: Offered cognitive training intervention after study ended.

Table 17. Patient-Level Nonpharmacologic Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Pop cat	Intervention type	Brief intervention group description	Duration, months	Brief control group description
Blumenthal, 2018[307] Fair	US	MCI	IG1: Exercise and diet counseling IG2: Exercise IG3: Diet counseling	IG1: Supervised exercise for 3 d/wk, 45-min/d over three months; unsupervised home exercise sessions 3 d/wk, 45min/d over subsequent three months; and dietary counseling for 1 d/wk, 30-min/d for three months and 2 d/month, 30-min/d over subsequent three months IG2: Supervised exercise for 3 d/wk, 45-min/d over three months; unsupervised home exercise sessions 3 d/wk, 45min/d over subsequent three months IG3: Dietary counseling for 1 d/wk, 30-min/d for three months and 2 d/month, 30-min/d over subsequent three months.	6	AC: Instructed to maintain their normal activities, and educational calls on CVD health-related topics 1 d/wk, 30-min/d for three months and 2 d/month for subsequent three months.
Burgener, 2008[312] Fair	US	Dem	Multicomponent	Multicomponent group-based intervention with exercise classes for 3 d/wk, 60 min/d and cognitive behavioral therapy and support groups 1 d/wk, 90 min/d over 5 months.	5	WL: Offered intervention after 5 months.
Fiatarone Singh, 2014*[278] Fair	AUS	MCI	IG1: Multicomponent IG2: Cognitive training	IG1: Computerized, group-based cognitive training ("COGPACK") and group-based progressive resistance training for 2 d/wk, 100 min/d over 6 months. IG2: Computerized, group-based cognitive training ("COGPACK") for 2 d/wk, 45 min/d over 6 months plus a 30 min of sham physical exercises of stretching and seated calisthenics during each session.	6	Sham: Sham cognitive training 2 d/wk, 30 min/d of watching videos and responding to questions regarding video content plus 30 min of sham physical exercises of stretching and seated calisthenics during each session.
Jha, 2013*[316] Fair	GBR	MCI + Dem	Other	Psychiatric assessment, counseling, and support for 1 d/month, 60 min/d over 6 months.	6	MI: General counseling to patient and caregiver (not focused on wellbeing or quality of life) for 1 d/month, 60 min/d over 6 months.
Karssemeijer, 2019[310] Fair	NLD	Dem	IG1: Multicomponent IG2: Exercise	IG1: Supervised combined cognitive-aerobic exercise sessions for 3 d/wk, 30-50 min/d for 3 months. IG2: Supervised aerobic exercise sessions for 3 d/wk, 30-50 min/d for 3 months.	3	Sham: Relaxation and stretching exercises for 3 d/week, 30-min/d over 3 months.

Table 17. Patient-Level Nonpharmacologic Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Pop cat	Intervention type	Brief intervention group description	Duration, months	Brief control group description
Marshall, 2015*[315] Fair	GBR	Dem	Other	Group-based psychotherapy and psychoeducation for 1 d/wk, 75 min/day over 2.5 months.	2.5	WL: Offered intervention after study ended.
Quinn, 2016*[314] Good	GBR	Dem	Other	Group-based self-management program for 1 d/wk, 90 min/d over 2 months.	2	UC: Routine memory clinic services including psychiatry, psychology, occupational therapy, and social services.
Richard, 2009[317] Fair	NLD	Dem	Other	Vascular care targeting hypercholesterolemia and hypertension including medications, exercise, diet and smoking cessation during outpatient visits every 3 months for 24 months.	24	UC: Physicians followed general guidelines for treatment for vascular risk factors in older adults.
Rovner, 2018[318]	US	MCI	Other	Five in-home 60-min behavioral activation (goal-setting and action plans) intervention over 4 months and six in-home 60-min followup maintenance sessions over subsequent 20 months.	4	Sham: Five in-home 60-min general supportive therapy sessions over 4 months and six in-home 60-min followup maintenance sessions over subsequent 20 months.
Shimada, 2017[321] Fair	JPN	MCI	Multicomponent	Group-based physical and cognitive exercises for 1 d/wk, 90 min/d over 9 months	9	MI: Three 90-minute health promotion classes and three booster calls over 9 months.
Straubmeier, 2017[322] Fair	DEU	MCI + Dem	Multicomponent	Multicomponent group-based intervention with social, cognitive, and physical components for 5 d/wk, 120-min/d over 6 months.	6	WL: Offered intervention after 6 months.
Train the Brain Consortium, 2017[319] Fair	ITA	MCI	Multicomponent	Multicomponent group-based intervention with twice daily 30-min/d cognitive training; music therapy 1 d/wk, 60-min/d; monthly 60-min movie and discussion sessions; and supervised exercise 3 d/wk, 60-min/d.	7	None: Maintain normal activities.
Wolfs, 2008[313] Fair	NLD	MCI + Dem	Other	Multidisciplinary diagnostic assessment with results and recommended treatment and management plan sent to general practitioner ("Diagnostic Observation Center for Psychogeriatric Patients" [DOC-PG]).	NR	UC: Diagnosis by general practitioner or outside service.

* New study

Abbreviations: AC = attention control; AUS = Australia; BI = brief intervention; CG = control group; d = day; Dem = dementia; DEU = Germany; ESP = Spain; FIN = Finland; FRA = France; GBR = Great Britain/United Kingdom; GRC = Greece; HKG = Hong Kong; ITA = Italy; JPN = Japan; KOR = Korea; MCI = mild cognitive impairment; MI = minimal intervention; min = minutes; NLD = Netherlands; NR = not reported; Pop cat = population category; UC = usual care; wk = week; WL = waitlist

Table 18. Patient-Level Nonpharmacologic Interventions: Summary of Results, by Intervention (KQ 4 and 5)

Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-Specific Cognitive Function	Physical Function	Quality of Life	Mental Health and Behavioral Symptoms	Other
Cognitive Stimulation, Training, and Rehabilitation											
Amieva, 2016*[275] Good	Dem	481	79	24	NR	IG1: ↔ (ADAS-Cog) IG2: ↔ (ADAS-Cog)	NR	IG1: ↔ (ADL/IADL) IG2: ↔ (ADL/IADL)	IG1: ↔ IG2: ↔	IG1: ↔ (D, NPS) IG2: ↔ (D, NPS)	IG1: ↔ (CGR Burden, Institutionalization, Dementia Incidence) IG2: ↔ (CGR Burden, Institutionalization, Dementia Incidence)
Belleville, 2018*[289] Fair	MCI	145	72	6	NR	NR	↔† (Memory)	↔ (ADL)	↔	↔ (A, D)	NR
Bergamaschi, 2013*[280] Fair	Dem	32	78	12	NR	↑ (MMSE)	↑ (EF) ↔† (Memory)	↑ (ADL), ↔ (IADL)	NR	↔ (D)	NR
Buschert, 2011[269] Fair	MCI + Dem	39	73	6	NR	MCI: ↑ (ADAS-Cog), ↔ (MMSE) Dem: ↔ (ADAS-Cog), ↔ (MMSE)	↔ (Attention) ↔ (EF) ↔ (Memory)	NR	MCI: ↔ Dem: ↔	MCI: ↑ (D) Dem: ↔ (D)	NR
Cahn-Weiner, 2003*[267] Good	Dem	34	77	3	NR	NR	↔ (Attention) ↔ (EF) ↔ (Language) ↔ (Memory)	↔ (ADL/IADL)	NR	NR	NR
Cavallo, 2016*[284] Good	Dem	80	76	6	NR	↔ (MMSE)	↑ (Attention) ↔† (EF) ↑ (Language) ↔† (Memory)	NR	NR	↔ (A, D)	NR
Chapman, 2004[266] Fair	Dem	54	76	12	↔	↔ (ADAS-Cog), ↔ (MMSE)	NR	↔ (ADL/IADL)	↔	↔ (NPS)	↑ (CGR Burden)
Cove, 2014*[277] Fair	Dem	72	77	3	NR	IG1: ↔ (ADAS-Cog), ↔ (MMSE)	NR	NR	IG1: ↔ IG2: ↔	NR	NR

Table 18. Patient-Level Nonpharmacologic Interventions: Summary of Results, by Intervention (KQ 4 and 5)

Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-Specific Cognitive Function	Physical Function	Quality of Life	Mental Health and Behavioral Symptoms	Other
						IG2: ↔ (ADAS-Cog), ↔ (MMSE)					
Fiatarone Singh, 2014[278] Fair	MCI	100	70	18	NR	IG2: ↔ (ADAS-Cog)	IG2: ↔ (EF), ↔ (Memory)	IG2: ↔ (IADL)	NR	NR	NR
Greenaway, 2012*[271] Fair	MCI	40	72	6	NR	↔ (MMSE)	↔ (Memory)	NR	↔	↔ (D)	↑ (CGR Burden, CGR MH [D]) ↔ (CGR QOL)
Herrera, 2012[281] Fair	MCI	22	77	6	NR	NR	↔† (Attention) ↔† (Memory)	NR	NR	NR	NR
Hyer, 2016*[285] Fair	MCI	77	75	5	NR	NR	↔† (EF) ↔ (Memory)	↑ (IADL)	NR	NR	NR
Jelcic, 2012*[282] Fair	Dem	40	82	3	NR	↑ (MMSE)	↔† (Attention) ↔ (EF) ↔† (Language) ↔† (Memory)	↔ (IADL)	NR	NR	NR
Jeong, 2016*[274] Fair	MCI	293	70	9	IG1: ↔ IG2: ↑	IG1: ↑ (ADAS-Cog), ↔ (MMSE) IG2: ↑ (ADAS-Cog), ↔ (MMSE)	IG1: ↔ (EF), ↔ (Memory) IG2: ↔ (EF), ↔ (Memory)	IG1: ↔ (IADL) IG2: ↔ (IADL)	IG1: ↔ IG2: ↑	IG1: ↔ (D), ↑ (NPS) IG2: ↔ (D), ↔ (NPS)	NR
Kallio, 2018*[288] Fair	Dem	147	83	9	NR	↔ (ADAS-Cog)	NR	NR	↔	NR	↔ (Deaths, Institutionalization, Hospitalization)
Kinsella, 2009[264] Fair	MCI	54	77	4	NR	NR	↔ (Memory)	NR	NR	NR	NR
Kurz, 2012[272] Fair	Dem	201	74	9	NR	↔ (MMSE)	NR	↔ (IADL)	↔	↔ (D), ↔ (NPS)	↔ (CGR Burden, CGR MH [D])
Nousia, 2018*[286] Fair	Dem	50	76	3.5	NR	NR	↑ (Attention) ↑ (EF) ↑ (Language) ↔† (Memory)	NR	NR	NR	NR
Olazaran, 2004[265] Fair	MCI + Dem	84	74	12	NR	↔ (ADAS-Cog), ↔ (MMSE)	NR	↔ (IADL)	NR	↑ (D)	NR
Orrell, 2014*[279] Good	Dem	236	83	6	NR	↔ (ADAS-Cog), ↔ (MMSE)	NR	↔ (ADL/IADL)	↑ (Self-rated), ↔ (Proxy-rated)	↔ (NPS)	↔ (CGR QOL)

Table 18. Patient-Level Nonpharmacologic Interventions: Summary of Results, by Intervention (KQ 4 and 5)

Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-Specific Cognitive Function	Physical Function	Quality of Life	Mental Health and Behavioral Symptoms	Other
Orrell, 2017*[273] Good	Dem	356	78	6	NR	↔ (ADAS-Cog), ↔ (MMSE)	NR	↔ (ADL/IADL)	↔	↔ (D), ↔ (NPS)	↔ (CGR QOL, CGR MH, CGR Burden)
Pantoni, 2017*[287] Fair	MCI	46	75	12	NR	↔ (MMSE)	↔ (Attention) ↔ (EF) ↔† (Memory)	↔ (ADL), ↔ (IADL), ↔ (ADL/IADL)	↔	↔ (D)	NR
Quayhagen, 1995[270] Fair	Dem	95	74	9	NR	↑ (MDRS)	NR	NR	NR	NR	NR
Rapp, 2002[268] Fair	MCI	19	74	6	NR	NR	↔† (Memory)	NR	NR	NR	NR
Troyer, 2008[262] Fair	MCI	54	75	6	NR	NR	↔† (Memory)	NR	NR	NR	NR
Tsantali, 2017*[283] Fair	Dem	63	74	12	NR	IG1: ↑ (MMSE) IG2: ↔ (MMSE)	IG1: ↑ (Language), ↑ (Memory) IG2: ↔ (Language), ↔† (Memory)	NR	NR	NR	NR
Tsolaki, 2011[263] Fair	MCI	196	68	6	NR	↑ (MMSE)	NR	↑ (ADL)	NR	NR	NR
Vidovich, 2015*[276] Good	MCI	160	75	24	NR	↔ (CAMCOG-R)	↔† (Attention) ↔ (EF) ↔ (Memory)	NR	↑	↔ (D)	↔ (Dementia Incidence)
Exercise Interventions											
Baker, 2010[296] Fair	MCI	33	70	6	NR	NR	↑ (Attention) ↑ (EF)	NR	NR	NR	NR
Blumenthal, 2019*[307] Fair	MCI	160	65	6	↔	NR	↔ (EF) ↔ (Language) ↔ (Memory)	NR	NR	NR	↔ (Dementia Incidence)
Dawson, 2016*[305] Fair	Dem	26	74	3	NR	NR	↔ (EF)	↔ (ADL/IADL)	NR	NR	↔ (Institutionalization)
Doi, 2017*[304] Good	MCI	201	76	9	NR	↑ (MMSE)	↔ (Attention) ↔ (EF) ↔† (Memory)	NR	NR	NR	↔ (Dementia Incidence)
Ho, 2018*[308] Fair	MCI + Dem	204	79	12	NR	NR	IG1: ↔ (Attention) ↔ (EF)	IG1: ↔ (IADL) IG2: ↔ (IADL)	NR	IG1: ↔ (D), ↔ (NPS)	NR

Table 18. Patient-Level Nonpharmacologic Interventions: Summary of Results, by Intervention (KQ 4 and 5)

Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-Specific Cognitive Function	Physical Function	Quality of Life	Mental Health and Behavioral Symptoms	Other
							↔ (Language) ↔ (Memory) IG2: ↔ (Attention) ↔ (EF) ↔ (Language) ↔ (Memory)			IG2; ↔ (D), ↔ (NPS)	
Hoffmann, 2016*[302] Good	Dem	200	70	4	NR	↔ (MMSE)	↔ (EF) ↔ (Language)	↔ (ADL/IADL)	↔	↔ (D) ↑ (NPS)	NR
Holthoff, 2015*[303] Fair	Dem	30	72	6	NR	↔ (MMSE)	↑ (EF)	↑ (ADL)	NR	↑ (NPS)	↔ (CGR Burden, Institutionalization)
Hong, 2017*[300] Fair	MCI	25	77	3	NR	↔ (MoCA)	↔† (Attention) ↔ (EF) ↔ (Memory)	NR	NR	NR	NR
Karssemeijer, 2019*[310] Fair	Dem	115	80	6	NR	NR	↔ (EF) ↔ (Memory)	NR	NR	NR	↔ (SAE)
Lam, 2011[293] Fair	MCI	389	78	5	↑	↔ (ADAS-Cog), ↔ (MMSE)	↔† (Attention) ↔ (EF) ↔ (Language) ↔ (Memory)	NR	NR	↔ (D), ↔ (NPS)	NR
Lamb, 2018*[306] Good	Dem	494	77	12	NR	↑ (ADAS-Cog)	NR	↔ (ADL/IADL)	↔ (Self-rated), ↔ (Proxy-rated)	↔ (NPS)	↔ (CGR Burden, CGR QOL)
Lautenschlager, 2008[292] Good	MCI	170	68	17	↑	↑ (ADAS-Cog)	↔ (Attention) ↔ (EF) ↔† (Memory)	NR	↔	↔ (D)	NR
Lazarou, 2017*[299] Fair	MCI	154	67	10	↑	↑ (MMSE)	↑ (Attention) ↔† (EF) ↑ (Memory)	NR	NR	↔ (NPS)	NR
Liu-Ambrose, 2016*[291] Fair	Dem	70	74	12	NR	↔ (ADAS-Cog)	↔ (EF)	↔ (ADL/IADL)	NR	NR	NR
Morris, 2017*[301] Good	MCI + Dem	76	73	6	NR	NR	↔ (EF) ↔ (Memory)	↑ (ADL/IADL)	NR	↔ (D)	NR

Table 18. Patient-Level Nonpharmacologic Interventions: Summary of Results, by Intervention (KQ 4 and 5)

Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-Specific Cognitive Function	Physical Function	Quality of Life	Mental Health and Behavioral Symptoms	Other
Pitkälä, 2013*[290] Good	Dem	210	78	12	NR	IG1: ↔ (MMSE) IG2: ↔ (MMSE)	IG1: ↔ (EF) IG2: ↔† (EF)	IG1: ↔ (ADL/IADL) IG2: ↑ (ADL/IADL)	NR	IG1: ↔ (D), ↔ (NPS) IG2: ↔ (D), ↔ (NPS)	IG1: ↔ (Institutionalization) IG2: ↔ (Institutionalization)
Schwenk, 2010[294] Fair	Dem	61	82	3	NR	NR	↔ (EF)	NR	NR	NR	NR
Siu, 2018*[309] Fair	MCI	160	NR	4	NR	↑ (MMSE)	NR	↑ (IADL)	NR	NR	NR
Suzuki, 2012[297] Fair	MCI	50	76	6	NR	↔ (ADAS-Cog), ↑ (MMSE)	↔† (Memory)	NR	NR	NR	NR
Venturelli, 2010[295] Fair	MCI + Dem	30	84	3	NR	↑ (MMSE)	NR	↑ (ADL)	NR	NR	NR
Vreugdenhil, 2012[298] Fair	Dem	40	74	4	NR	↑ (ADAS-Cog), ↑ (MMSE)	NR	↑ (ADL/IADL)	NR	↔ (D)	↔ (CGR Burden)
Multicomponent and Other Interventions											
Bae, 2019*[320] Fair	MCI	83	76	6	NR	↔ (MMSE)	↔ (Attention) ↔ (EF) ↔† (Memory)	NR	NR	↔ (D)	↔ (AE, SAE)
Belleville, 2018*[289] Fair	MCI	145	72	6	NR	NR	↔ (Memory)	↔ (ADL)	↔	↔ (A, D)	NR
Blumenthal, 2019*[307] Fair	MCI	160	65	6	IG1: ↔ IG3: ↔	NR	IG1: ↑ (EF) ↔ (Language) ↔ (Memory) IG3: ↔ (EF) ↔ (Language) ↔ (Memory)	NR	NR	NR	IG1: ↔ (Dementia Incidence) IG3: ↔ (Dementia Incidence)
Bellantonio, 2008[311] Fair	Dem	100	82	9	NR	NR	NR	NR	NR	NR	↔ (Institutionalization)
Burgener, 2008[312] Fair	Dem	43	77	5	NR	↔ (MMSE)	NR	NR	NR	↔ (D)	NR

Table 18. Patient-Level Nonpharmacologic Interventions: Summary of Results, by Intervention (KQ 4 and 5)

Author, year Quality	Pop cat	N rand	Age, mean	FU (mo.)	Global Function	Global Cognitive Function	Domain-Specific Cognitive Function	Physical Function	Quality of Life	Mental Health and Behavioral Symptoms	Other
Fiatarone Singh, 2014[278] Fair	MCI	100	70	18	NR	IG1: ↔ (ADAS-Cog)	IG1: ↔ (EF), ↔ (Memory)	IG1: ↔ (IADL)	NR	NR	NR
Jha, 2013*[316] Fair	MCI + Dem	48	79	6	NR	↔ (MMSE)	NR	NR	↔ (EQ-5D), ↑ (WHO-5)	↔ (D)	↔ (CGR Burden)
Karssemeijer, 2019*[310] Fair	Dem	115	80	6	NR	NR	↔ (EF) ↔ (Memory)	NR	NR	NR	↔ (SAE)
Marshall, 2015*[315] Fair	Dem	58	76	5	NR	↔ (MMSE)	NR	NR	↔	↔ (D)	↔ (CGR MH [Psych Health])
Quinn, 2016*[314] Good	Dem	24	76	6	NR	NR	NR	NR	↔	↔ (A, D)	NR
Richard, 2009[317] Fair	Dem	123	76	24	NR	↔ (MMSE)	NR	↔ (ADL/IADL)	NR	↔ (NPS)	↔ (Institutionalization)
Rovner, 2018*[318] Good	MCI	221	76	24	NR	↔ (MMSE)	↔ (Attention) ↑ (EF) ↔ (Language) ↔† (Memory)	NR	NR	↔ (D)	↔ (Hospitalization, ER visits) ↔ (Dementia Incidence)
Shimada, 2018*[321] Fair	MCI	308	72	9	NR	↑ (MMSE)	↔† (EF) ↔† (Memory)	NR	NR	NR	↔ (AE, Falls, Hospitalization)
Straubmeier, 2017*[322] Fair	MCI + Dem	453	81	6	NR	↑ (MMSE)	NR	↑ (ADL)	NR	↔ (NPS)	↔ (AE)
Train the Brain Consortium, 2017*[319] Fair	MCI	113	74	7	NR	↑ (ADAS-Cog)	↔ (Attention) ↔† (EF) ↔ (Memory)	NR	NR	NR	↔ (AE)
Wolfs, 2008[313]	MCI + Dem	230	78	12	↔	↔ (MMSE)	NR	↔ (IADL)	↔	↔ (D, NPS)	

NOTE: Arrows represent study-reported results.

Symbol Legend:
↑ = Statistically significant between-group difference in favor of intervention group
↔ = No statistically significant difference between groups or no clear between-group difference (not reported).

Table 18. Patient-Level Nonpharmacologic Interventions: Summary of Results, by Intervention (KQ 4 and 5)

* New study
† Mixed results from multiple tests assessing same cognitive domain

Abbreviations: A = Anxiety; ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive subscale; ADL = Activities of Daily Living; AE = adverse events; D = Depression; Dem = Dementia; EF = executive functioning; FU (mo.) = followup (months); CGR = caregiver; IADL = Instrumental Activities of Daily Living; MCI = mild cognitive impairment; MH = mental health; MMSE = Mini-Mental State Examination; NPS = Composite neuropsychiatric symptoms; NR = not reported; N rand = number of participants randomized; Pop cat = population category; Psych = psychological; QOL = quality of life; SAE = serious adverse events

Table 19. Caregiver and Caregiver-Patient Dyad Interventions: Study Characteristics, by Intervention (KQ 4 and 5)

Author, year (study name)	Quality	Country	Audience	N rand	Caregiver age, mean	Caregiver type	Caregiver female, %	Patient BL MMSE, mean
Psychoeducation Interventions								
Barnes, 2018*[325]	Fair	GBR	Caregiver	55	67	Spouse: 67 Child: 29 Other: 4	77	24
Belle, 2006[326] (REACH II)	Fair	US	Caregiver	642	61	Spouse: 43 Child: 48 Other: 9	83	13.0
Berwig, 2017*[327] (GE-REACH)	Fair	DEU	Caregiver	92	73	Spouse: 89 Child: NR Other: 11	66	12.4
Brennan, 1995[328]	Fair	US	Caregiver	102	60	Spouse: 68 Child: 28 Other: NR	67	NR
Bruvik, 2013*[329]	Good	NOR	Caregiver + Patient	230	64	Spouse: 53 Child: 40 Other: 7	77	21.2
Burgio, 2003[330] (REACH - Birmingham)	Fair	US	Caregiver	140	63	Spouse: 50 Child: NR Other: 50	79	13.0
Chang, 1999[331]	Fair	US	Caregiver	87	66	Spouse: 89 Child: NR Other: NR	NR	NR
Chu, 2011[332]	Fair	TWN	Caregiver	85	NR	Spouse: 32 Child: 64 Other: NR	57	NR
Coon, 2003[333]	Fair	US	Caregiver	169	64	Spouse: 57 Child: 43 Other: NR	100	14.2
Cristancho-Lacroix, 2015*[334]	Fair	FRA	Caregiver	49	62	Spouse: 37 Child: 59 Other: 4	65	18.7
De Rotrou, 2011[335]	Fair	FRA	Caregiver	157	65	Spouse: 57 Child: 29 Other: NR	68	NR
Ducharme, 2011[336]	Fair	CAN	Caregiver	121	61	Spouse: 34 Child: 52 Other: 14	79	NR
Duggleby, 2018*[337] (MT4C)	Fair	CAN	Caregiver	199	64	Spouse: 49 Child: 46 Other: 5	81	NR
Finkel, 2007[338]	Fair	US	Caregiver	46	65	Spouse: 44 Child: 53 Other: NR	68	NR
Fung, 2002*[339]	Fair	HKG	Caregiver	60	NR	Spouse: 50 Child: 29 Other: 21	63	NR
Gallagher-Thompson, 2003[340] (REACH - Palo Alto)	Fair	US	Caregiver	257	57	Spouse: NR Child: NR Other: NR	100	13.7
Gallagher-Thompson, 2008[341]	Fair	US	Caregiver	184	58	Spouse: 38 Child: NR Other: 62	100	14.1
Gallagher-Thompson, 2010*[342]	Good	US	Caregiver	76	59	Spouse: 13 Child: NR Other: NR	87	NR

Table 19. Caregiver and Caregiver-Patient Dyad Interventions: Study Characteristics, by Intervention (KQ 4 and 5)

Author, year (study name)	Quality	Country	Audience	N rand	Caregiver age, mean	Caregiver type	Caregiver female, %	Patient BL MMSE, mean
Garand, 2014*[343]	Fair	US	Caregiver	73	65	Spouse: 75 Child: NR Other: NR	78	NR
Gaugler, 2013*[344] (NYUCI-AC)	Fair	US	Family	107	50	Spouse: 0 Child: 100 Other: 0	94	NR
Gitlin, 2001[345]	Fair	US	Caregiver	202	60	Spouse: 25 Child: NR Other: 75	73	NR
Gitlin, 2003[347] (REACH - Philadelphia)	Fair	US	Caregiver	255	61	Spouse: 35 Child: NR Other: NR	74	12.2
Gitlin, 2008[346]	Fair	US	Caregiver + Patient	60	65	Spouse: 62 Child: 38 Other: 0	88	11.6
Gitlin, 2010[348] (ACT)	Fair	US	Caregiver	272	66	Spouse: 51 Child: NR Other: NR	82	13.0
Gitlin, 2010[460] (COPE)	Fair	US	Caregiver + Patient	237	62	Spouse: 38 Child: NR Other: 62	89	13.4
Graff, 2006[349]	Fair	NLD	Caregiver + Patient	135	64	Spouse: 58 Child: 32 Other: 10	70	19.0
Hebert, 2003[350]	Fair	CAN	Caregiver	144	60	Spouse: 61 Child: NR Other: NR	80	NR
Hepburn, 2005[351]	Fair	US	Caregiver	215	66	Spouse: 66 Child: NR Other: NR	76	17.7
Joling, 2012[352]	Fair	NLD	Family	192	70	Spouse: 94 Child: NR Other: NR	70	12.6
Judge, 2013*[353] (ANSWERS)	Fair	US	Caregiver + Patient	128	65	Spouse: 60 Child: NR Other: NR	74	23.0
Koivisto, 2016*[354] (ALSOVA)	Fair	FIN	Caregiver + Patient	236	66	Spouse: 70 Child: 23 Other: 6	66	21.5
Kurz, 2010[355] (AENEAS)	Fair	AUT, DEU, CHE	Caregiver	292	62	Spouse: 58 Child: 38 Other: NR	69	13.9
Kwok, 2013*[356]	Fair	HKG	Caregiver	42	NR	Spouse: 10 Child: 87 Other: 3	71	NR
Laakkonen, 2016*[357]	Fair	FIN	Caregiver + Patient	136	75	Spouse: 100 Child: 0 Other: 0	62	20.8
Livingston, 2013*[358] (START)	Good	GBR	Caregiver	260	59	Spouse: 42 Child: 44 Other: 15	68	NR
Losada, 2010[359]	Fair	ESP	Caregiver	167	60	Spouse: 35 Child: 59 Other: 6	83	NR

Table 19. Caregiver and Caregiver-Patient Dyad Interventions: Study Characteristics, by Intervention (KQ 4 and 5)

Author, year (study name)	Quality	Country	Audience	N rand	Caregiver age, mean	Caregiver type	Caregiver female, %	Patient BL MMSE, mean
Mariott, 2000[360]	Fair	GBR	Caregiver	28	64	Spouse: 52 Child: 41 Other: 7	69	12.5
Martin-Carrasco, 2009[362]	Fair	ESP	Caregiver	115	58	Spouse: 55 Child: 36 Other: 9	69	18.7
Martin-Carrasco, 2014*[361] (EDUCA-II)	Fair	ESP	Caregiver	238	62	Spouse: 49 Child: 45 Other: 6	77	12.9
Martin-Cook, 2005[363]	Fair	US	Caregiver + Patient	49	NR	Spouse: 92 Child: 6 Other: 2	70	19.4
Martindale-Adams, 2013*[364] (CONNECT)	Fair	US	Caregiver	154	66	Spouse: 72 Child: 23 Other: 5	84	15.4
Mittelman, 2004*[365] (NYUCI)	Fair	US	Family	406	71	Spouse: 100 Child: 0 Other: 0	60	NR
Nunez-Naveira, 2016*[366]	Fair	DNK, POL, ESP	Caregiver	77	NR	Spouse: NR Child: NR Other: NR	64	NR
Ostwald, 1999[367]	Fair	US	Caregiver + Patient	117	66	Spouse: 66 Child: 28 Other: NR	65	NR
Roberts, 1999[368]	Fair	CAN	Caregiver	77	62	Spouse: 52 Child: 45 Other: NR	70	NR
Schoenmakers, 2010[369]	Fair	BEL	Caregiver	62	63	Spouse: 46 Child: 34 Other: 20	76	NR
Steffen, 2016*[371]	Good	US	Caregiver	74	60	Spouse: 52 Child: 43 Other: 10	100	NR
Spaulding-Wilson, 2018*[370]	Fair	US	Caregiver	104	63	Spouse: 45 Child: 52 Other: 3	73	NR
Teri, 2005[372]	Fair	US	Caregiver	95	65	Spouse: 55 Child: 31 Other: 14	70	13.6
Tremont, 2015*[373]	Fair	US	Caregiver	250	63	Spouse: 51 Child: 42 Other: 7	78	NR
Ulstein, 2007[374]	Fair	NOR	Caregiver	180	65	Spouse: 70 Child: 28 Other: NR	64	20.8
Voigt-Radloff, 2011[375]	Fair	DEU	Caregiver + Patient	141	65	Spouse: 56 Child: 37 Other: 6	71	20.4
Waldorff, 2012[376] (DAISY)	Good	DNK	Caregiver + Patient	330	66	Spouse: 65 Child: 26 Other: 9	67	24.1
Wang, 2011*[377]	Fair	HKG	Caregiver + Patient	80	41	Spouse: 40 Child: 38 Other: 22	65	17.4

Table 19. Caregiver and Caregiver-Patient Dyad Interventions: Study Characteristics, by Intervention (KQ 4 and 5)

Author, year (study name)	Quality	Country	Audience	N rand	Caregiver age, mean	Caregiver type	Caregiver female, %	Patient BL MMSE, mean
Williams, 2010[378]	Fair	US	Caregiver	116	60	Spouse: 41 Child: 50 Other: 9	78	NR
Wilz, 2016*[379]	Fair	DEU	Caregiver	176	62	Spouse: NR Child: NR Other: NR	82	NR
Wilz, 2018*[380] (Tele.TAnDem)	Good	DEU	Caregiver	273	64	Spouse: 60 Child: 38 Other: 2	81	NR
Wright, 2001[381]	Fair	US	Caregiver	93	60	Spouse: 45 Child: 38 Other: 17	76	NR
Care/Case Management Interventions								
Bass, 2003[382]	Fair	US	Caregiver + Patient	182	NR	Spouse: NR Child: NR Other: NR	NR	NR
Callahan, 2006[383]	Fair	US	Caregiver + Patient	153	61	Spouse: 44 Child: 36 Other: 20	89	18.0
Chien, 2008*[385]	Fair	HKG	Family	88	44	Spouse: 32 Child: 36 Other: 32	64	17.4
Chien, 2011*[384]	Good	HKG	Caregiver + Patient	92	45	Spouse: 27 Child: 39 Other: 34	66	NR
Chu, 2000[386]	Fair	CAN	Caregiver + Patient	75	NR	Spouse: NR Child: NR Other: NR	73	22.8
Eloniemi-Sulkava, 2009[388]	Good	FIN	Caregiver + Patient	125	75	Spouse: 100 Child: 0 Other: NR	62	13.8
Eloniemi-Sulvaka, 2001[387]	Fair	FIN	Caregiver + Patient	100	64	Spouse: 56 Child: 34 Other: 10	69	14.8
Fortinsky, 2009[389]	Fair	US	Caregiver + Patient	84	62	Spouse: 45 Child: 46 Other: 9	69	NR
Jansen, 2011[390]	Fair	NLD	Caregiver + Patient	99	63	Spouse: 40 Child: 48 Other: 9	70	22.3
Lam, 2010[391]	Fair	HKG	Caregiver + Patient	102	NR	Spouse: 29 Child: 60 Other: NR	74	17.8
Mavandadi, 2017*	Fair	US	Caregiver + Patient	75	70	Spouse: 83 Child: NR Other: NR	97	NR
Meewsen, 2012[393] (AD-Euro)	Good	NLD	Caregiver + Patient	175	64	Spouse: 54 Child: 41 Other: 5	70	22.7
Menn, 2012[394]	Fair	DEU	Caregiver + Patient	390	59	Spouse: 32 Child: 59 Other: 9	73	18.7
Samus, 2014*[395] (MIND)	Fair	US	Caregiver + Patient	303	67	Spouse: 43 Child: 48 Other: 9	75	19.1

Table 19. Caregiver and Caregiver-Patient Dyad Interventions: Study Characteristics, by Intervention (KQ 4 and 5)

Author, year (study name)	Quality	Country	Audience	N rand	Caregiver age, mean	Caregiver type	Caregiver female, %	Patient BL MMSE, mean
Thyrian, 2017*[396] (DelpHi)	Fair	DEU	Caregiver + Patient	516	NR	Spouse: NR Child: NR Other: NR	NR	22.8
Vickrey, 2006[397]	Good	US	Caregiver + Patient	408	66	Spouse: 55 Child: 39 Other: 6	69	NR
Xiao, 2016*[398]	Fair	AUS	Caregiver	72	56†	Spouse: 26 Child: NR Other: NR	84	NR
Other Interventions								
Charlesworth, 2008[399]	Fair	GBR	Caregiver	236	68	Spouse: 67 Child: NR Other: NR	64	NR
Connell, 2009[400]	Fair	US	Caregiver	157	67	Spouse: 100 Child: 0 Other: NR	100	NR
Gitlin, 2018*[401] (TAP-VA)	Fair	US	Caregiver + patient	160	72	Spouse: 87 Child: NR Other: 13	98	16.6
Hirano, 2011[402]	Fair	JPN	Caregiver	36	74	Spouse: NR Child: NR Other: NR	68	18.3
King, 2002[403]	Fair	US	Caregiver	100	63	Spouse: 53 Child: 47 Other: 0	100	NR
Leach, 2015*[404] (TRANSCENDENT)	Good	AUS	Caregiver	17	66	Spouse: 65 Child: 35 Other: 5	88	NR
LoGiudice, 1999[405]	Fair	AUS	Caregiver + Patient	50	61	Spouse: 54 Child: 36 Other: 10	78	17.0
Nourhashemi, 2010[406] (PLASA)	Fair	FRA	Caregiver + Patient	1131	NR	Spouse: NR Child: NR Other: NR	NR	19.7
Pillemer, 2002[407]	Fair	US	Caregiver	147	58	Spouse: 40 Child: 60 Other: 0	71	NR
Prick, 2015*[408]	Fair	NLD	Caregiver + Patient	111	72	Spouse: 90 Child: NR Other: 10	72	21.0
Spijker, 2011[409]	Good	NLD	Caregiver	301	59	Spouse: 28 Child: 52 Other: 6	73	NR
Teri, 2003[410]	Good	US	Caregiver + Patient	153	NR	Spouse: NR Child: NR Other: NR	NR	16.7
Winter, 2006[411]	Fair	US	Caregiver	103	67	Spouse: 41 Child: NR Other: NR	100	NR

* New study
† Median

Abbreviations: ACT = Advancing Caregiver Training; AENEAS = A European Network for the Evaluation of Alzheimer Support groups; ALSOVA = Alzheimer's Disease Follow-up Study; ANSWERS = Acquiring New Skills While Enhancing Remaining Strengths; AUS = Australia; AUT = Austria; BL = baseline; BEL = Belgium; CAN = Canada; CHE = Chile;

Table 19. Caregiver and Caregiver-Patient Dyad Interventions: Study Characteristics, by Intervention (KQ 4 and 5)

CONNECT = Telephone Support for Dementia Caregivers; COPE = Care of Persons with Dementia in their Environments; DAISY = Danish Alzheimer Intervention Study; DelpHi = Dementia: Life- and Person-Centered Help in Mecklenburg-Western Pomerania; DEU = Germany; DNK = Denmark; ESP = Spain; FIN = Finland; FRA = France; GBR = Great Britain/United Kingdom; GE-REACH = German Adaptation of Resources for Enhancing Alzheimer's Caregiver Health; HKG = Hong Kong; JPN = Japan; MIND = Maximizing Independence at Home; MT4C = My Tools 4 Care; N rand = number of participants randomized; NLD = Netherlands; NOR = Norway; NR = not reported; NYUCI = New York University Caregiver Intervention; NYUCI-AC = New York University Caregiver Intervention-Adult Child; PLASA = Plan de Soin et d'Aide dans la maladie d'Alzheimer or "Specific Care and Assistance Plan for Alzheimer Disease"; POL = Poland; REACH = Resources for Enhancing Alzheimer's Caregiver Health; START = STrAtegies for RelaTives; TAP-VA = Tailored-Activity Program-Veterans Affairs; Tele.TAnDem = Telephone-based CBT for Family Caregivers of People With Dementia; TRANSCENDENT = Transcendental Meditation for the improvement of health and wellbeing in community-dwelling dementia caregivers; TWN = Taiwan

Table 20. Caregiver and Caregiver-Patient Dyad Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Intervention type	Audience	Brief intervention group description	Duration, months	Brief control group description
Psychoeducation Interventions						
Barnes, 2018*[325] Fair	GBR	Individual psychoeducation	Caregiver	Individual home-based psychoeducation sessions for 3 d/2 months, 60-min/d	2	BI: One 60-min general support session to discuss any issues identified at the point of referral.
Belle, 2006[326] Fair	US	Individual psychoeducation	Caregiver	Individual- and group-based psychoeducation and support through nine 90-min in-home sessions and three 30-min telephone sessions plus 5 structured telephone support group sessions over 6 months.	6	BI: Educational materials and two 15-min phone calls.
Berwig, 2017*[327] Fair	DEU	Individual psychoeducation	Caregiver	Individual psychoeducation, problem-solving, and social support through nine 90-min in-home sessions and three 30-min telephone sessions over 6 months.	6	UC: Care as usual corresponding with available services determined by German Care Insurance.
Brennan, 1995[328] Fair	US	Telehealth psychoeducation	Caregiver	Computer-based psychoeducation program and moderated support ("ComputerLink") with access 24 h/d, 7 d/wk. over 1 year.	12	BI: In-person training on identifying local services and resources
Bruvik, 2013*[329] Good	NOR	Individual psychoeducation	Caregiver + Patient	Individual- and group-based psychoeducation and support through five 60-min individual counseling sessions, 2 half-day seminars, and six 2-hr group meetings over 12 months.	12	BI: Information on local services.
Burgio, 2003[330] Fair	US	Individual psychoeducation	Caregiver	Individualized psychoeducation through one 3-hr group workshop, eleven 60-min in-home sessions, and five 15-min phone calls over 1 year.	12	BI: Minimal support control delivered through five 15-min telephone calls focused on empathetic and active listening and generic educational materials.
Chang, 1999[331] Fair	US	Telehealth psychoeducation	Caregiver	Videos demonstrating assisted modeling behaviors specific to dressing and eating plus reinforcing telephone calls 1 d/wk over 12 weeks.	3	MI: Telephone calls on same schedule as intervention (1 d/wk over 12 weeks) to assess general well-being, but offered no specific strategies for dressing or eating.
Chu, 2011[332] Fair	TWN	Group-based psychoeducation	Caregiver	Group-based psychoeducation and support through 12 weekly group sessions over 3 months.	3	UC: Standard care provided in Taiwan (not described).
Coon, 2003[333] Fair	US	IG1: Group-based psychoeducation IG2: Group-based psychoeducation	Caregiver	IG1: Group-based psychoeducation focused on anger management through 8 weekly 120-min sessions over 4 months. IG2: Group-based psychoeducation focused on depression management through 8 weekly 120-min sessions over 4 months.	4	WL: Offered either anger management or depression management intervention after study ended.

Table 20. Caregiver and Caregiver-Patient Dyad Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Intervention type	Audience	Brief intervention group description	Duration, months	Brief control group description
Cristancho-Lacroix, 2015*[334] Fair	FRA	Telehealth psychoeducation	Caregiver	Computer-based psychoeducation program and support ("Diapason") with 12 sessions intended for 1 d/wk, 15-30 min/d for 3 months.	3	WL: Offered intervention after study ended.
De Rotrou, 2011[335] Fair	FRA	Group-based psychoeducation	Caregiver	Group-based psychoeducation through 12 weekly 120-min sessions over 3 months.	3	WL: Offered intervention after study ended.
Duggleby, 2018*[337] Fair	CAN	Individual psychoeducation	Caregiver	Self-administered web-based psychoeducation for 3 months	3	WL: Participants received a copy of the publicly available Alzheimer's Society's "The Progression of Alzheimer's Disease" booklet via email and were offered access to the intervention website after three months.
Ducharme, 2011[336] Fair	CAN	Individual psychoeducation	Caregiver	Individual-based "Learning to Become a Family Caregiver" program consisting of psychoeducation sessions for 1 d/wk, 90 min/d over 7 weeks.	2	UC: Usual care provided by memory clinics including referrals to local services.
Finkel, 2007[338] Fair	US	Telehealth psychoeducation	Caregiver	Computer- and telephone-based psychoeducation and moderated support ("Computer-Telephone Integration System") including 2 in-home sessions and 12 sessions conducted via computer/telephone over 6 months.	6	BI: Basic educational materials and 2 brief telephone check-in calls.
Fung, 2002*[339] Fair	HKG	Group-based psychoeducation	Caregiver	Group-based psychoeducation program through 12 weekly 60-min sessions over 3 months.	3	UC: Standard family services provided by dementia care center (Hong Kong) including culturally tailored medical assessment and treatment, advice and referrals to social welfare services, and monthly educational talks in dementia care and social and recreational activities
Gallagher-Thompson, 2003[340] Fair	US	Group-based psychoeducation	Caregiver	Group-based "Coping with Caregiving" psychoeducation class through 10 weekly 120-min group sessions followed by 8 monthly 120-min booster sessions over 10 months.	10	MI: Written educational materials and brief, regularly scheduled empathetic telephone support calls.
Gallagher-Thompson, 2008[341] Fair	US	Group-based psychoeducation	Caregiver	Group-based "Coping with Caregiving" psychoeducation class through 12 weekly 120-min classes over 4 months.	4	MI: Written educational materials and seven 15-30 min empathetic telephone support calls.
Gallagher-Thompson, 2010*[342] Good	US	Telehealth psychoeducation	Caregiver	Culturally-tailored psychoeducational/ cognitive behavioral skill training program delivered via 150 min DVD with 3 telephone check-in calls.	3	AC: General 150-min DVD on dementia with 3 telephone check-in calls.

Table 20. Caregiver and Caregiver-Patient Dyad Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Intervention type	Audience	Brief intervention group description	Duration, months	Brief control group description
Garand, 2014*[343] Fair	US	Individual psychoeducation	Caregiver	Individual problem-solving therapy including 6 in-person sessions, 90 min/session over 3 months followed by 3 telephone contacts, 45 min/call over 1.5 months.	4.5	AC: In-person and telephone counseling focused on nutrition following same schedule as intervention (6 in-person sessions and 3 telephone contacts).
Gaugler, 2013*[344] Fair	US	Family-based psychoeducation	Family	"New York University Caregiver Intervention - adapted for adult child caregivers" consisting of 6 individual and family counseling sessions, support group participation, and ad hoc counseling in-person or via phone or e-mail over 4 months.	4	MI: Biannual project newsletter and quarterly check-in calls including ad hoc consultations as necessary.
Gitlin, 2001[345] Fair	US	Individual psychoeducation	Caregiver	Individual in-person psychoeducation sessions and home environmental modifications during five 90-min biweekly home visits over 3 months.	3	UC: Usual care not described; given education materials and booklet describing home environmental safety tips after study was over.
Gitlin, 2003[347] Fair	US	Individual psychoeducation	Caregiver	Individual-based "Environment Skill-Building Program" including psychoeducation, problem-solving training, and adaptive equipment provided through five 90-min home visits and one 30-min telephone call over 6 months followed by maintenance sessions over another 6 months.	12	UC: Usual care not described; given information on local resources.
Gitlin, 2008[346] Fair	US	Individual psychoeducation	Caregiver + Patient	Individual-based "Tailored Activity Program" including customized activities to address neuropsychiatric and functional needs through six 90-min home visits and two 150-min telephone contacts over 4 months.	4	WL: Offered intervention after study ended.
Gitlin, 2010[460] Fair	US	Individual psychoeducation	Caregiver + Patient	Individual-based intervention including assessments, caregiver education, and caregiver training for up to 10 occupational therapy home visits and 1 in-person and 1 telephone call with a nurse over 4 months.	4	MI: Up to 3 20-min telephone calls and mailed materials.
Gitlin, 2010[348] Fair	US	Individual psychoeducation	Caregiver	Individual-based "Advancing Caregiver Training" consisting of activities to address patient-, caregiver-, and environmental-based needs through up to 9 occupational therapy visits, 1 in-home and 1 telephone nursing session, and 3 brief telephone contacts over 4 months.	6	None: Offered 2-hr in-home workshop involving education and tips for managing problem behaviors after study ended.
Graff, 2006[349] Fair	NLD	Individual psychoeducation	Caregiver + Patient	In-home, individual-based occupational therapy during ten 60-min sessions over 5 weeks.	1	WL: Offered intervention after study ended.

Table 20. Caregiver and Caregiver-Patient Dyad Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Intervention type	Audience	Brief intervention group description	Duration, months	Brief control group description
Hebert, 2003[350] Fair	CAN	Group-based psychoeducation	Caregiver	Group-based psychoeducation through 15 weekly 120-min sessions over 4 months.	4	UC: Referred to regular support group program offered by local Alzheimer's Society (Canada) or health care organizations in their region.
Hepburn, 2005[351] Fair	US	Group-based psychoeducation	Caregiver	"Partners in Caregiving" group-based psychoeducation program through 6 weekly 120-min sessions over 6 weeks.	1.5	WL: Offered intervention after study ended.
Joling, 2012[352] Fair	NLD	Family-based psychoeducation	Family	Family- and individual-based counseling through 2 individual counseling session and 4 family counseling sessions over 1 year.	12	UC: Standard care provided by the Netherland's community health services, which does not include support groups.
Judge, 2013*[353] Fair	US	Individual psychoeducation	Caregiver + Patient	Individual-based "ANSWERS" psychoeducation and cognitive rehabilitation program consisting of six 90-min individual sessions over 3 months.	3	BI: Standardized education resource packet and information on local resources.
Koivisto, 2016*[354] Fair	FIN	Group-based psychoeducation	Caregiver + Patient	Group-based psychoeducation and support through 4 group-based courses (for 16 days total) over 2 years.	24	UC: Basic counseling by a memory nurse at time of diagnosis and followed up with their normal healthcare system.
Kurz, 2010[355] Fair	AUT, DEU, CHE	Group-based psychoeducation	Caregiver	Group-based psychoeducation through 7 bi-weekly 90-min sessions and 6 bi-monthly refresher sessions over 15 months.	15	UC: One standard individual counseling session.
Kwok, 2013*[356] Fair	HKG	Telehealth psychoeducation	Caregiver	Telephone-based psychoeducation and training for 1 d/wk, 30 min/d plus educational DVD over 12 weeks.	3	BI: Educational DVD about dementia caregiving.
Laakkonen, 2016*[357] Fair	FIN	Group-based psychoeducation	Caregiver + Patient	Group-based psychoeducation and support through 8 weekly 4-hr sessions over 8 weeks.	2	UC: Standard care provided by Finnish health and social service system.
Livingston, 2013*[358] Good	GBR	Individual psychoeducation	Caregiver	Individual-based "START" psychoeducation and support program consisting of eight 60-min in-home sessions over 2-3 months.	2-3	UC: Standard care for the family member with dementia including pharmacologic and nonpharmacologic treatment and caregiver support.
Losada, 2010[359] Fair	ESP	Group-based psychoeducation	Caregiver	Group-based psychoeducation through 12 weekly 90-120-min sessions over 3 months.	3	UC: Standard care or assistance provided by social and health centers in Spain plus offered intervention after study ended.
Mariott, 2000[360] Fair	GBR	Individual psychoeducation	Caregiver	Individual-based psychoeducation during 14 sessions every other week over 7 months.	7	None: No intervention.
Martin-Carrasco, 2009[362] Fair	ESP	Individual psychoeducation	Caregiver	Individual-based "Psychoeducational Intervention Program" through eight 90-min sessions over 4 months.	4	UC: Standard care for caregivers including information on dementia and local resources and on-demand in-person and phone support.

Table 20. Caregiver and Caregiver-Patient Dyad Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Intervention type	Audience	Brief intervention group description	Duration, months	Brief control group description
Martin-Carrasco, 2014*[361] Fair	ESP	Group-based psychoeducation	Caregiver	Group-based "Psychoeducational Intervention Program" consisting of 7 sessions, 90-120-min each over 3 months.†	3	UC: Standard care from day center or memory clinic including information for caregivers.
Martin-Cook, 2005[363] Fair	US	Individual psychoeducation	Caregiver + Patient	Individual-based psychoeducation through 4 weekly sessions over 1 month.	1	WL: Given information on local resources and offered intervention after study ended.
Martindale-Adams, 2013*[364] Fair	US	Telehealth psychoeducation	Caregiver	Telephone-based, group psychoeducation and support through fourteen 60-min telephone group sessions plus workbook over 12 months.	12	BI: General print materials on dementia and safety and information on local resources; offered intervention workbook and one workshop after study ended.
Mittelman, 2004*[365] Fair	US	Family-based psychoeducation	Family	Family- and individual-based counseling through two 60-180-min individual counseling sessions and four 60-180-min family counseling sessions, weekly support groups, and ad hoc counseling as needed over 4 months.	≥4	UC: Standard services provided by the NYU Alzheimer's Disease Center including information and advice on request plus access to same support groups and ad hoc counseling provided to intervention group.
Nunez-Naveira, 2016*[366] Fair	DNK, POL, ESP	Telehealth psychoeducation	Caregiver	App-based psychoeducation and support ("UnderstAID application") with 5 different learning modules, a calendar and note-taking section, a moderated social networking section, and options for receiving personalized feedback.	3	None: No intervention.
Ostwald, 1999[367] Fair	US	Group-based psychoeducation	Caregiver + Patient	"Minnesota Family Workshop" group-based psychoeducation program through 7 weekly 120-min sessions over 7 weeks.	3	WL: Offered intervention after study ended.
Roberts, 1999[368] Fair	CAN	Individual psychoeducation	Caregiver	Individual-based problem-solving training through up to 10 in-home or telephone sessions over 6 months.	6	UC: Access to community and respite services by other nurses and volunteer agencies.
Schoenmakers, 2010[369] Fair	BEL	Individual psychoeducation	Caregiver	Individual-based support to support home care through 4 home visits and 12 telephone calls over 1 year and ad-hoc care counselor support.	12	UC: Access to usual care systems.
Spaulding-Wilson, 2018*[370] Fair	US	Group-based psychoeducation	Caregiver	Group-based psychoeducation delivered in a 2 day workshop.	0.07	WL: Offered intervention after study ended.
Steffen, 2016*[371] Good	US	Telehealth psychoeducation	Caregiver	Video- and telephone-based psychoeducation consisting of ten 30-min video segments, a workbook, and ten telephone calls over 14 weeks.	3	MI: Basic education and support via an Alzheimer's Basic Care Guide and seven 20-min telephone calls every other week.

Table 20. Caregiver and Caregiver-Patient Dyad Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Intervention type	Audience	Brief intervention group description	Duration, months	Brief control group description
Teri, 2005[372] Fair	US	Individual psychoeducation	Caregiver	Individual-based psychoeducation program "STAR-Caregivers" consisting of 8 weekly in-home treatment sessions followed by 4 monthly phone calls over 6 months.	6	UC: Standard medical care including nonspecific advice and support routinely provided by nurses and primary physicians or community support services with no specific behavior-management training.
Tremont, 2015*[373] Fair	US	Telehealth psychoeducation	Caregiver	Individual, telephone-based psychoeducation provided over sixteen 30-60 min calls over 6 months.	6	MI: Non-directive telephone support following same schedule as intervention (sixteen 30-60 min calls over 6 months).
Ulstein, 2007[374] Fair	NOR	Group-based psychoeducation	Caregiver	Group-based psychoeducation consisting of one 3-hr educational program and six 2-hr group meetings over 4.5 months.	4.5	UC: Patients received standard memory clinic care and caregivers were offered to talk with an experienced nurse and offered advice and ad hoc counseling as needed.
Voigt-Radloff, 2011[375] Fair	DEU	Individual psychoeducation	Caregiver + Patient	Individual-based psychoeducation and support through three home visits and two telephone calls over 1 year.	1.25	MI: Usual care and 60 min of community occupational therapy consultation.
Waldorff, 2012[376] Good	DNK	Group-based psychoeducation	Caregiver + Patient	Individual- and group-based psychoeducation and support through up to 7 individual counseling sessions for both patient and caregiver, five 2-hr educational group courses, and up to 8 followup phone calls over 8-12 months.	8-12	BI: General information and guidance about dementia and information and referral to local resources at 6 and 12 months.
Wang, 2011*[377] Fair	HKG	Group-based psychoeducation	Caregiver + Patient	Group-based psychoeducation program "Family Mutual Support Programme in Dementia Care" through 8 bi-weekly 120-min sessions over 6 months.	6	UC: Standard family services provided by dementia care center (Hong Kong) including culturally tailored medical assessment and treatment, advice and referrals to social welfare services, and monthly educational talks in dementia care and social and recreational activities.
Williams, 2010[378] Fair	US	Telehealth psychoeducation	Caregiver	Video- and telephone-based psychoeducation consisting of ten 7-10-min video segments, a workbook, and five telephone calls over 5 weeks.	1.25	WL: Offered intervention after study ended.
Wilz, 2016*[379] Fair	DEU	Telehealth psychoeducation	Caregiver	Telephone-based psychoeducation and training through seven 60-min sessions over 3 months; first session was in home and remaining six sessions were via telephone.	3	BI: Written educational material on dementia, dementia caregiving, and local resources.
Wilz, 2018*[380] Good	DEU	Telehealth psychoeducation	Caregiver	Telephone-based psychoeducation and training through 12 50-min sessions over 6 months.	6	UC: Written educational material about dementia and caregiving.

Table 20. Caregiver and Caregiver-Patient Dyad Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Intervention type	Audience	Brief intervention group description	Duration, months	Brief control group description
Wright, 2001[381] Fair	US	Individual psychoeducation	Caregiver	Individual-based psychoeducation and support through three home visits and two telephone calls over 1 year.	12	None: No intervention.
Care/Case Management Interventions						
Bass, 2003[382] Fair	US	Care/Case Management + Psychoeducation	Caregiver + Patient	Partnership between local Alzheimer's Association and managed care plan to provide care consultation and individualized treatment plans to families over 1 year through regular telephone calls (12 calls per year on average).	12	UC: Standard care provided by managed care and ability to contact Alzheimer's Association on their own.
Callahan, 2006[383] Fair	US	Care/Case Management + Psychoeducation	Caregiver + Patient	Care management for patients and caregivers including pharmacotherapy treatment and individualized caregiver psychoeducation and support through monthly in-person sessions and telephone-based support groups over 1 year.	12	MI: Augmented usual care including 40-90 min of counseling by geriatric nurse practitioner, written consultation note to PCP communicating results of diagnostic assessment, and materials describing local resources.
Chien, 2008*[385] Fair	HKG	Care/Case Management + Psychoeducation	Family	Care management for patients and caregivers including assessment, education, support, and referrals including twelve 2-hr group sessions and monthly home visits over 6 months.	6	MI: Routine care provided by Hong Kong Dementia Care Center including pharmacotherapy, social and recreational activities, and materials for caregivers plus 6 monthly psychoeducation group sessions for caregivers.
Chien, 2011*[384] Good	HKG	Care/Case Management + Psychoeducation	Caregiver + Patient	Dementia Family Care Programme including assessment, education, support, and referrals including ten 2-hr individual sessions.	6	MI: Routine care provided by Hong Kong Dementia Care Center including pharmacotherapy, social and recreational activities, and materials for caregivers plus 6 monthly psychoeducation group sessions for caregivers.
Chu, 2000[386] Fair	CAN	Care/Case Management + Psychoeducation	Caregiver + Patient	Multicomponent "Early Home Care Program" including case management with education, referrals to community services, ongoing monitoring, supportive counseling, and skills training through monthly in-person or telephone contacts in addition to conventional home care (occupational and physical therapy, respite care, personal care assistance, social work, nursing) over 1.5 years.	18	UC: Conventional home care program provided by local Canadian Home Care Program, but not including case management.

Table 20. Caregiver and Caregiver-Patient Dyad Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Intervention type	Audience	Brief intervention group description	Duration, months	Brief control group description
Eloniemi-Sulkava, 2009[388] Good	FIN	Care/Case Management + Psychoeducation	Caregiver + Patient	Multicomponent support with family care coordinator, geriatrician medical assessments and treatment, support groups, and individualized services through group sessions over 2 years.	24	UC: Standard services provided for geriatric patients in Finland community care by the municipal social and healthcare system or private sector.
Eloniemi-Sulvaka, 2001[387] Fair	FIN	Care/Case Management + Psychoeducation	Caregiver + Patient	Comprehensive support provided by a "Dementia Family Care Coordinator" through counseling, in-home visits, annual courses, facilitating care plans, and arranging social and health care services over 2 years.	24	UC: Standard services provided for geriatric patients in Finland community care by the municipal social and healthcare system or private sector.
Fortinsky, 2009[389] Fair	US	Care/Case Management + Psychoeducation	Caregiver + Patient	Partnership between local Alzheimer's Association and primary care physicians to provide care consultation and individualized treatment plans to families through monthly contact over 1 year.	12	UC: Standard primary care plus package of educational materials.
Jansen, 2011[390] Fair	NLD	Care/Case Management + Psychoeducation	Caregiver + Patient	Case management including assessment, advice and information, planning, coordinating, organizing collaboration, and monitoring of care provided through home visits and telephone calls over 1 year.	12	UC: Standard health care and welfare services in the Netherlands.
Lam, 2010[391] Fair	HKG	Care/Case Management + Psychoeducation	Caregiver + Patient	Case management including assessment and advice, cognitive stimulation, coordination with geriatricians, and referrals to local social services provided through home visits and telephone calls over 4 months.	4	MI: One home visit focused on home safety, with no case management.
Mavandadi, 2017*[392] Fair	US	Care/Case Management + Psychoeducation	Caregiver + Patient	Care management including assessment and advice, education, support, and coordination through monthly telephone calls over 3 months.	3	UC: Standard care through VA and mailed general materials about VA and community resources for patients and caregivers.
Meewsen, 2012[393] Good	NLD	Care/Case Management + Psychoeducation	Caregiver + Patient	Care coordination and post-diagnosis treatment provided by memory clinic.	12	UC: Usual care coordination and post-diagnosis treatment provided only by general practitioner.
Menn, 2012[394] Fair	DEU	IG1: Care/Case Management + Psychoeducation IG2: Care/Case Management + Psychoeducation	Caregiver + Patient	IG1: Training for primary care physicians on evidence-based treatment for dementia plus physician suggested that caregiver attend support groups and receive counseling for up to 2 years. IG2: Training for primary care physicians on evidence-based treatment for dementia plus	24	UC: General training course on dementia care for physicians and usual dementia medical treatment.

Table 20. Caregiver and Caregiver-Patient Dyad Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Intervention type	Audience	Brief intervention group description	Duration, months	Brief control group description
				physician suggested that caregiver attend support groups and receive counseling for up to 1 year.		
Samus, 2014*[395] Fair	US	Care/Case Management + Psychoeducation	Caregiver + Patient	Dementia Care Needs Assessment and care coordination including two home visits and monthly contact with families over 18 months.	18	MI: Received results of Dementia Care Needs Assessment, recommendations for each unmet need, and brief resource guide with local and national aging organizations.
Thyrian, 2017*[396] Fair	DEU	Care/Case Management + Psychoeducation	Caregiver + Patient	Care management and interdisciplinary collaboration including assessment and individualized treatment plans, medication management, and caregiver support including 6 home visits over 6 months and ongoing telephone support for remaining 6 months.	12	UC: Usual primary care provided to patients and caregivers in Germany (not described).
Vickrey, 2006[397] Good	US	Care/Case Management + Psychoeducation	Caregiver + Patient	Care coordination for 18 months including communication within and between organizations, Internet-based care management, collaborative care planning with caregivers, caregiver self-management support, ongoing follow-up, and provider education.	18	UC: Usual care provided by primary care clinics.
Xiao, 2016*[398] Fair	AUS	Care/Case Management + Psychoeducation	Caregiver	Extending usual care coordination for patient to also support caregivers through quarterly home visits and monthly telephone calls over 1 year.	12	UC: Care coordination for patient provided as part of usual care in Australia and optional activities for caregivers including monthly support group meetings and information sessions.
Other Interventions						
Charlesworth, 2008[399] Fair	GBR	Social support	Caregiver	"Befriending" intervention matching trained volunteers with caregivers to provide emotional and informational support through weekly home visits over at least 6 months.	6	UC: Standard care provided by local health, social, or voluntary services.
Connell, 2009[400] Fair	US	Physical activity counseling	Caregiver	"Health First" video- and telephone-based counseling to encourage physical activity provided through 14 telephone calls over 6 months.	6	None: No intervention.
Gitlin, 2018*[401] Fair	US	Multidisciplinary assessment	Caregiver + patient	Multidisciplinary assessment and tailored care plan involving 8 treatment sessions over 4 months.	4	MI: Biweekly telephone-based dementia education sessions (8 30-min contacts) over 4 months.

Table 20. Caregiver and Caregiver-Patient Dyad Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Intervention type	Audience	Brief intervention group description	Duration, months	Brief control group description
Hirano, 2011[402] Fair	JPN	Physical activity counseling	Caregiver	One-time prescription to participate in moderate-intensity physical activity 3 times per week over the course of 3 months.	3	MI: Carried a pedometer that recorded daily steps and asked to record their daily progress of exercise amount in a journal.
King, 2002[403] Fair	US	Physical activity counseling	Caregiver	Prescription to participate in moderate-intensity physical activity at least 4 d/wk, 30-40 min/d provided through weekly and then monthly telephone calls plus daily logs over 12 months.	12	AC: Nutrition education provided at same intensity as intervention (weekly and then monthly telephone calls) over 12 months.
Leach, 2015*[404] Good	AUS	Other	Caregiver	Transcendental Meditation® program delivered in-person through twelve 30-90 min sessions over 3 months.	3	None: Offered 4-week healthy lifestyle education program (4 weekly 90-min sessions) after study ended.
LoGiudice, 1999[405] Fair	AUS	Assessment and Treatment Planning	Caregiver + Patient	Attended hospital memory clinic on 2 occasions for assessment and referral to appropriate services.	NR	UC: Patients received same medical and cognitive assessments and caregivers received same interview as intervention group and all questions were answered and referrals back to primary care physician were encouraged.
Nourhashemi, 2010[406] Fair	FRA	Multidisciplinary assessment and treatment plan	Caregiver + Patient	Multidisciplinary assessment and tailored care plan once every 6 months over 24 months.	24	UC: Standard medical care provided at community health centers.
Pillemer, 2002[407] Fair	US	Social support	Caregiver	"Peer Support Project" providing one-on-one peer support through up to 8 weekly 120-min visits over 2 months.	2	None: No intervention.
Prick, 2015*[408] Fair	NLD	Multicomponent dyadic	Caregiver + Patient	Multicomponent dyadic intervention including exercise training, psychoeducation, communication skills training and pleasant skills training through eight 1-hr in-home sessions over 3 months.	3	BI: Monthly mailings with general information and 3 monthly 10-min telephone calls to provide emotional support.
Spijker, 2011[409] Good	NLD	Provider training	Caregiver	"Systematic Care Program for Dementia" consisting of training professionals in the assessment of and strategies for reducing caregiver burden including screening, psychosocial support, and care coordination with medical, home, and respite care.	12	UC: Standard care provided by the Netherland's community mental health services (not described).
Teri, 2003[410] Good	US	Multicomponent dyadic	Caregiver + Patient	Multicomponent dyadic intervention including an exercise intervention for patients and caregiver psychoeducation through twelve 60-min in-home visits over the first 3 months and three 60-min followup sessions over the next 3 months.	6	UC: Monthly mailings with general information and 3 monthly 10-min telephone calls to provide emotional support.

Table 20. Caregiver and Caregiver-Patient Dyad Interventions: Intervention Characteristics, by Intervention (KQ 4 and 5)

Author, year Quality	Country	Intervention type	Audience	Brief intervention group description	Duration, months	Brief control group description
Winter, 2006[411] Fair	US	Social support	Caregiver	Telephone-based group social support through 26 weekly telephone calls over 6 months.	6	None: No intervention.

* New study

† Based on "Coping with Caregiving" Intervention tested in Gallagher-Thompson, 2003 and Gallagher-Thompson, 2008

Abbreviations: AC = attention control; AUS = Australia; AUT = Austria; BI = brief intervention; BL = baseline; BEL = Belgium; CAN = Canada; CHE = Chile; DEU = Germany; d = day; DNK = Denmark; ESP = Spain; FIN = Finland; FRA = France; GBR = Great Britain/United Kingdom; HKG = Hong Kong; hr = hour; IG = intervention groups; JPN = Japan; MI = minimal intervention; min = minute; NLD = Netherlands; NOR = Norway; NR = not reported; NYU = New York University; POL = Poland; TWN = Taiwan; UC = usual care; wk = week; WL = waitlist

Table 21. Caregiver and Caregiver-Patient Dyad Interventions: Summary of Results, by Intervention (KQ 4 and 5)

Author, year Quality	Intervention Type	N rand	FU (mo.)†	Caregiver Burden	Caregiver Mental Health Symptoms	Caregiver QOL	Patient Institutionalization	Patient Mental Health and Behavioral Symptoms	Other Patient Outcomes
Psychoeducation Interventions									
Barnes, 2018*[325] Fair	Individual psychoeducation	55	3	NR	↔ (A, D)	↔	NR	NR	NR
Belle, 2006[326] Fair	Individual psychoeducation	642	6	NR	↑ (D)	NR	↔	NR	NR
Berwig, 2017*[327] Fair	Individual psychoeducation	92	9	↑	↔ (A, D)	↔	NR	↑ (NPS)	NR
Brennan, 1995[328] Fair	Telehealth psychoeducation	102	12	↔	↔ (D)	NR	NR	NR	NR
Bruvik, 2013*[329] Good	Individual psychoeducation	230	12	NR	↔ (D)	NR	NR	↔ (D)	NR
Burgio, 2003[330] Fair	Individual psychoeducation	140	6	Black: ↔ White: ↔	Black: ↔ (A, D) White: ↔ (A, D)	NR	NR	Black: ↔ (NPS) White: ↔ (NPS)	NR
Chang, 1999[331] Fair	Telehealth psychoeducation	87	3	NR	↔ (A, D)	NR	NR	NR	↔ (ADL)
Chu, 2011[332] Fair	Group-based psychoeducation	85	4	↔	↑ (D)	NR	NR	NR	NR
Coon, 2003[333] Fair	Group-based psychoeducation	169	6	NR	IG1: ↔ (D) IG2: ↔ (D)	NR	NR	NR	NR
Cristancho-Lacroix, 2015*[334] Fair	Telehealth psychoeducation	49	6	↔	↔ (D, PS)	NR	NR	↔ (NPS)	NR
De Rotrou, 2011[335] Fair	Group-based psychoeducation	157	6	↔	↔ (D)	NR	NR	↔ (NPS)	↔ (GCF), ↔ (ADL/IADL)
Ducharme, 2011[336] Fair	Individual psychoeducation	121	8	↔	NR	NR	NR	NR	NR
Duggleby, 2018*[337] Fair	Individual psychoeducation	199	6	NR	NR	↔	NR	NR	NR
Finkel, 2007[338] Fair	Telehealth psychoeducation	46	6	↔	↔ (D)	NR	NR	NR	NR
Fung, 2002*[339] Fair	Group-based psychoeducation	60	4	↑	NR	↑	↔	NR	NR

Table 21. Caregiver and Caregiver-Patient Dyad Interventions: Summary of Results, by Intervention (KQ 4 and 5)

Author, year Quality	Intervention Type	N rand	FU (mo.)†	Caregiver Burden	Caregiver Mental Health Symptoms	Caregiver QOL	Patient Institutionalization	Patient Mental Health and Behavioral Symptoms	Other Patient Outcomes
Gallagher-Thompson, 2003[340] Fair	Group-based psychoeducation	257	6	Hisp: ↔ White: ↔	Hisp: ↔ (D) White: ↔ (D)	NR	NR	NR	NR
Gallagher-Thompson, 2008[341] Fair	Group-based psychoeducation	184	6	Hisp: ↔ White: ↔	Hisp: ↔ (D, PS) White: ↔ (D, PS)	NR	NR	NR	NR
Gallagher-Thompson, 2010*[342] Good	Telehealth psychoeducation	76	4	↑	↔ (D)	NR	NR	↔ (NPS)	NR
Garand, 2014*[343] Fair	Individual psychoeducation	73	12	NR	MCI pt: ↑ (A, D) Dem pt: ↑ (A, D)	NR	NR	NR	NR
Gaugler, 2013*[344] Fair	Family-based psychoeducation	107	18/36	↑	↑ (D)	↔	↑	↔ (NPS)	NR
Gitlin, 2001[345] Fair	Individual psychoeducation	202	3	↔	NR	NR	NR	↔ (NPS)	↔ (ADL, IADL)
Gitlin, 2003[347] Fair	Individual psychoeducation	255	6	↔	↔ (D)	NR	NR	↔ (NPS)	↔ (ADL, IADL)
Gitlin, 2008[346] Fair	Individual psychoeducation	60	4	↔	↔ (D)	NR	NR	↔ (D, NPS)	↔ (Pt QOL)
Gitlin, 2010[348] Fair	Individual psychoeducation	272	4	NR	NR	NR	NR	NR	↑ (ADL/IADL), ↔ (ADL), ↑ (IADL)
Gitlin, 2010[460] Fair	Individual psychoeducation	237	6	↑	↑ (D)	NR	NR	NR	NR
Graff, 2006[349] Fair	Individual psychoeducation	135	3	NR	↑ (D, PM)	↑	NR	↑ (D)	↑ (ADL/IADL)
Hebert, 2003[350] Fair	Group-based psychoeducation	144	4	↔	↔ (A)	NR	NR	↔ (NPS)	NR
Hepburn, 2005[351] Fair	Group-based psychoeducation	215	12	↔	NR	NR	NR	NR	NR
Joling, 2012[352] Fair	Family-based psychoeducation	192	17	NR	↔ (A, D)	NR	NR	NR	NR
Judge, 2013*[353] Fair	Individual psychoeducation	128	3	NR	↑ (D)	↔	NR	NR	NR

Table 21. Caregiver and Caregiver-Patient Dyad Interventions: Summary of Results, by Intervention (KQ 4 and 5)

Author, year Quality	Intervention Type	N rand	FU (mo.)†	Caregiver Burden	Caregiver Mental Health Symptoms	Caregiver QOL	Patient Institutionalization	Patient Mental Health and Behavioral Symptoms	Other Patient Outcomes
Koivisto, 2016*[354] Fair	Group-based psychoeducation	236	36	NR	NR	NR	↔	NR	NR
Kurz, 2010[355] Fair	Group-based psychoeducation	292	15	NR	↔ (D)	↔	↔	NR	NR
Kwok, 2013*[356] Fair	Telehealth psychoeducation	42	3	↑	NR	NR	NR	NR	NR
Laakkonen, 2016*[357] Fair	Group-based psychoeducation	136	9	NR	NR	↔	NR	NR	NR
Livingston, 2013*[358] Good	Individual psychoeducation	260	24	NR	↔ (A, D, PM)	NR	NR	NR	↔ (Pt QOL)
Losada, 2010[359] Fair	Group-based psychoeducation	167	3	NR	↑ (D)	NR	NR	NR	NR
Mariott, 2000[360] Fair	Individual psychoeducation	28	12	NR	↑ (D, PM)	NR	NR	↔ (D)	↔ (GCF), ↑ (ADL/IADL)
Martin-Carrasco, 2009[362] Fair	Individual psychoeducation	115	10	↑	↑ (PM)	↑‡	NR	NR	NR
Martin-Carrasco, 2014*[361] Fair	Group-based psychoeducation	238	4	↔	↔ (PM)	↔	NR	NR	NR
Martin-Cook, 2005[363] Fair	Individual psychoeducation	49	4	↔	↔ (D)	NR	NR	NR	
Martindale-Adams, 2013*[364] Fair	Telehealth psychoeducation	154	12	↔	↔ (D)	NR	NR	NR	NR
Mittelman, 2004*[365] Fair	Family-based psychoeducation	406	48/60	↑	↑ (D)	NR	↑	↔ (NPS)	NR
Nunez-Naveira, 2016*[366] Fair	Telehealth psychoeducation	77	3	NR	↔ (D)	NR	NR	NR	NR
Ostwald, 1999[367] Fair	Group-based psychoeducation	117	5	↔	↑ (D)	NR	NR	↔ (NPS)	↔ (GCF)

Table 21. Caregiver and Caregiver-Patient Dyad Interventions: Summary of Results, by Intervention (KQ 4 and 5)

Author, year Quality	Intervention Type	N rand	FU (mo.)†	Caregiver Burden	Caregiver Mental Health Symptoms	Caregiver QOL	Patient Institutionalization	Patient Mental Health and Behavioral Symptoms	Other Patient Outcomes
Roberts, 1999[368] Fair	Individual psychoeducation	77	12	↔	NR	NR	NR	NR	NR
Schoenmakers, 2010[369] Fair	Individual psychoeducation	62	12	NR	↑ (D)	NR	NR	NR	NR
Steffen, 2016*[371] Good	Telehealth psychoeducation	74	9	↑	↑ (A, D)	NR	NR	NR	NR
Spaulding-Wilson, 2018*[370] Fair	Group-based psychoeducation	104	6	↔	↑ (PS), ↔ (A, D)	NR	NR	NR	NR
Teri, 2005[372] Fair	Individual psychoeducation	95	6	↑	↑ (D)	NR	NR	↔ (NPS)	↔ (Pt QOL)
Tremont, 2015*[373] Fair	Telehealth psychoeducation	250	6	↑	↑ (D)	↔	↔	NR	NR
Ulstein, 2007[374] Fair	Group-based psychoeducation	180	12	NR	↔ (PS)	NR	↔	↔ (NPS)	NR
Voigt-Radloff, 2011[375] Fair	Individual psychoeducation	141	6, 12	NR	↔ (D)	↔	↔	↔ (D)	↔ (ADL/IADL), ↔ (Pt QOL)
Waldorff, 2012[376] Good	Group-based psychoeducation	330	36	NR	↔ (D)	↔	↔	↔ (D, NPS)	↔ (GCF), ↑ (ADL/IADL), ↔ (Pt QOL)
Wang, 2011*[377] Fair	Group-based psychoeducation	80	6	↑	NR	↑	NR	NR	↔ (GCF)
Williams, 2010[378] Fair	Telehealth psychoeducation	116	6	NR	↔ (A, D, PS)	NR	NR	NR	NR
Wilz, 2016*[379] Fair	Telehealth psychoeducation	176	6	NR	↔ (D)	NR	NR	NR	NR
Wilz, 2018*[380] Good	Telehealth psychoeducation	273	12	NR	↔ (D)	↔	NR	NR	NR
Wright, 2001[381] Fair	Individual psychoeducation	93	12	↔	↔ (D)	NR	↔	NR	NR
Care/Case Management Interventions									
Bass, 2003[382] Fair	Care/Case Management	182	12	NR	↑ (D)	NR	NR	NR	NR
Callahan, 2006[383] Fair	Care/Case Management	153	17	↔	↑ (D)	NR	↔	↔ (D), ↑ (NPS)	↔ (GCF), ↔ (ADL/IADL)

Table 21. Caregiver and Caregiver-Patient Dyad Interventions: Summary of Results, by Intervention (KQ 4 and 5)

Author, year Quality	Intervention Type	N rand	FU (mo.)†	Caregiver Burden	Caregiver Mental Health Symptoms	Caregiver QOL	Patient Institutionalization	Patient Mental Health and Behavioral Symptoms	Other Patient Outcomes
Chien, 2008*[385] Fair	Care/Case Management	88	12	↑	NR	↑	↑	↑ (NPS)	↔ (GCF)
Chien, 2011*[384] Good	Care/Case Management	92	18	↑	NR	↑	↑	↑ (NPS)	↔ (GCF)
Chu, 2000[386] Fair	Care/Case Management	75	17	↔	NR	NR	↔	NR	NR
Eloniemi-Sulkava, 2009[388] Good	Care/Case Management	125	24	NR	NR	NR	↔§	NR	NR
Eloniemi-Sulvaka, 2001[387] Fair	Care/Case Management	100	12	NR	NR	NR	↔	NR	NR
Fortinsky, 2009[389] Fair	Care/Case Management	84	12	↔	↔ (D)	NR	↔	NR	NR
Jansen, 2011[390] Fair	Care/Case Management	99	12	↔	↔ (D)	↔	NR	NR	↔ (Pt QOL)
Lam, 2010[391] Fair	Care/Case Management	102	12	↑	↔ (PM)	↔	NR	↔ (D, NPS)	↔ (GCF), ↔ (Pt QOL)
Mavandadi, 2017*[392] Fair	Care/Case Management	75	6	↑	NR	NR	NR	↔ (NPS)	NR
Meewsen, 2012[393] Good	Care/Case Management	175	12	NR	↑ (A, D)	↔	NR	↔ (D)	↔ (GCF), ↔ (ADL/IADL)
Menn, 2012[394] Fair	Care/Case Management	390	24	↔	NR	NR	IG1: ↔ IG2: ↔	NR	IG1: ↔ (GCF), ↔ (ADL), ↔ (IADL), ↔ (Pt QOL) IG2: ↔ (GCF), ↔ (ADL), ↔ (IADL), ↔ (Pt QOL)
Samus, 2014*[395] Fair	Care/Case Management	303	12, 18	↔	↔ (D)	↔	↑	↔ (D, NPS)	↑ (Pt QOL)
Thyrian, 2017*[396] Fair	Care/Case Management	516	12	↑	NR	NR	↔	↑ (D)	↔ (GCF), ↔ (ADL/IADL), ↔ (Pt QOL)
Vickrey, 2006[397] Good	Care/Case Management	408	17	NR	NR	↔	NR	NR	↑ (Pt QOL)

Table 21. Caregiver and Caregiver-Patient Dyad Interventions: Summary of Results, by Intervention (KQ 4 and 5)

Author, year Quality	Intervention Type	N rand	FU (mo.)†	Caregiver Burden	Caregiver Mental Health Symptoms	Caregiver QOL	Patient Institutionalization	Patient Mental Health and Behavioral Symptoms	Other Patient Outcomes
Xiao, 2016*[398] Fair	Care/Case Management	72	12	↑	NR	↑	NR	↔ (NPS)	NR
Other Interventions									
Charlesworth, 2008[399] Fair	Social support	236	22	NR	↔ (A, D)	↔	↔	NR	NR
Connell, 2009[400] Fair	Physical activity counseling	157	12	↔	↔ (D, PS)	NR	NR	NR	NR
Gitlin, 2018*[401] Fair	Multidisciplinary assessment	160	8	↔	↔ (D)	NR	NR	↔ (NPS)	↔ (AE), ↔ (PF), ↔ (Pt QOL)
Hirano, 2011[402] Fair	Physical activity counseling	36	3	↑	NR	NR	NR	↔ (NPS)	NR
King, 2002[403] Fair	Physical activity counseling	100	12	↔	↔ (A, D, PS)	NR	NR	↔ (NPS)	NR
Leach, 2015*[404] Good	Other	17	6	NR	NR	↔	NR	NR	NR
Logiudice, 1999[405] Fair	Assessment and treatment planning	50	12	↔	↔ (PM)	NR	↔	NR	NR
Nourhashemi, 2010[406] Fair	Multidisciplinary assessment and treatment plan	1131	22	NR	NR	NR	↔	NR	↔ (ADL/IADL)
Pillemer, 2002[407] Fair	Social support	147	6	NR	NR	NR	NR	NR	NR
Prick, 2015*[408] Fair	Multicomponent dyadic	111	6	↔	↔ (D)	NR	↔	↔ (D), ↑ (NPS)	↔ (Pt QOL)
Spijker, 2011[409] Good	Provider training	301	12	NR	NR	NR	↔	NR	NR
Teri, 2003[410] Good	Multicomponent dyadic	153	6, 17, 24	NR	↔ (D)	NR	↔	↔ (D)	↑ (Pt QOL)
Winter, 2006[411] Fair	Social support	103	6	↔	↔ (D)	NR	NR	NR	NR

NOTE: Arrows represent study-reported results.

Symbol Legend:
↑ = Statistically significant between-group difference in favor of intervention group
↔ = No statistically significant difference between groups or no clear between-group difference (not reported).
↓= Statistically significant between-group difference in favor of control group

Table 21. Caregiver and Caregiver-Patient Dyad Interventions: Summary of Results, by Intervention (KQ 4 and 5)

* New study
† Longest followup. Some studies have more than one FU listed because longest followup differed by outcome
‡ Statistically significantly favored IG on 7 of 8 subscales of the SF-36
§ Results statistically significant for at least one timepoint

Abbreviations: A = anxiety; ADL = Activities of Daily Living; D = depression; DEM = dementia; FU = followup; GCF = global cognitive function; Hisp = Hispanic; IADL = IADL = Instrumental Activities of Daily Living; IG = intervention group; MCI = mild cognitive impairment; mo. = months; NPS = Composite neuropsychiatric symptoms; NR = not reported; N rand = number of participants randomized; PM = psychological morbidity; PS = perceived stress; Pt = patient; QOL = quality of life;

Table 22. Summary of Evidence

Key Question Instrument or Treatment	Studies (k) Study Designs, Observations (n)	Summary of Findings	Consistency and Precision*	Other Limitations	Strength of Evidence*	Applicability
KQ 1	k=0	NA	NA	NA	NA	NA
KQ 2 Very brief instruments	k=31 cross sectional studies (6 new) n=22,359	25 instruments. To detect dementia sensitivity was usually at 0.75 or higher and specificity at 0.80 or higher. Across all very brief instruments, the detection of MCI was less consistent, with a wide range in sensitivity and specificity.	Reasonably consistent and precise (dementia) Inconsistent and imprecise (MCI)	Large number of instruments with little replication.	Moderate evidence of adequate sensitivity and specificity	Broad inclusion of older adult populations with a wide range of underlying dementia and MCI
KQ 2 Brief instruments	k=48 cross sectional studies (7 new) n=29,950	20 instruments. For the MMSE, to detect dementia, 15 studies (n=12,796) resulted in a pooled sensitivity of 0.89 (95% CI, 0.85 to 0.92) and a specificity of 0.89 (95% CI, 0.85 to 0.93). For other brief instruments reported in more than one study, sensitivity ranged from 0.74 to 1.0 and specificity ranged from 0.65 to 0.96. Across all brief instruments, the detection of MCI was less consistent, with a wide range in sensitivity and specificity.	Reasonably consistent and precise (dementia) Inconsistent and imprecise (MCI)	Large number of instruments with little replication, except for the MMSE.	Moderate evidence of adequate sensitivity and specificity	Broad inclusion of older adult populations with a wide range of underlying dementia and MCI. Administration time less useful for primary care screening.
KQ 2 Longer, self-administered instruments	k=8 cross sectional studies (0 new) n=2,271	4 instruments. Only the IQCODE was assessed in more than one study, with sensitivity to detect dementia ranging from 0.80 to 0.88 and specificity ranging from 0.51 to 0.91. To detect MCI, sensitivity ranged from 0.71 to 0.82 and specificity ranged from 0.69 to 0.92.	Reasonably consistent (dementia and MCI) Precise (dementia and MCI)	Few instruments, little replication.	Moderate evidence of adequate sensitivity and specificity	Broad inclusion of older adult populations with a wide range of underlying dementia and MCI
KQ 3	k=0	NA	NA	NA	NA	NA

Table 22. Summary of Evidence

Key Question Instrument or Treatment	Studies (k) Study Designs, Observations (n)	Summary of Findings	Consistency and Precision*	Other Limitations	Strength of Evidence*	Applicability
KQ 4 AChEIs and memantine	k=48 RCTs (6 new) n=22,431	Medications may improve measures of global cognitive function in short-term, but magnitude of differences between drug versus placebo groups was small. Pooled results indicate differences in change ranging from approximately 1 to 2.5 points in favor of drug groups on the ADAS-Cog-11 (range 0-70). For donepezil: MD, -2.13 95% CI: -0.94 to -3.32, k=6, n=1,981, I^2=64.4%). For galantamine: MD, -2.13 (95% CI, -1.32 to -2.94, k=9, n=3,786, I=65.9). For rivastigmine: -2.43 (95% CI: -0.75 to -4.10, k=5, n=2,618, I^2=81.9%). For memantine: -0.88 (95% CI: -0.11 to -1.65, k=8, n=2,609, I2=78.1%). Using accepted thresholds of clinical benefit, the average benefit across patients is not clinically significant. AChEIs and memantine increased the likelihood of improving or maintaining patient's global function (e.g., using a CIBIC+) by 15 percent (for memantine) to 50 percent (for rivastigmine) in the short-term (pooled 95% CI range, 0.49 to 2.69). Pooled continuous change found small effect sizes (SMDs ranging from 0.14 to 0.46). Other important measures such as mental health and neuropsychiatric symptoms and rates of institutionalization were rarely reported; no trials included measures of QOL.	Reasonably consistent Precise	Evidence of a small studies effect for the pooled result for global cognitive function measured by the MMSE for donepezil, indicating the possibility of publication bias. Few trials included followup longer than 6 months.	Moderate evidence of a small benefit	Older adults with dementia (mainly AD), particularly among those with moderate versus mild forms. Unclear representation of ethnic minorities and those of varying education levels. Doses of medications applicable to common use.
KQ 4 Other medications and supplements	k=29 RCTs (5 new) n=6,489	No evidence that antihypertensives, vitamins or omega-3 fatty acids, gonadal steroids, HMG-CoA reductase inhibitors, or NSAIDS are beneficial for any cognitive, functional or other outcome at 3 months to 4 years of followup.	Reasonably consistent Imprecise	Small trials often with differential attrition between groups. Lack of consistency in formulations and dosages of agents used.	Low evidence of no benefit	Older adults with mild to moderate dementia. Unclear representation of ethnic minorities and those of varying education levels.

Table 22. Summary of Evidence

Key Question Instrument or Treatment	Studies (k) Study Designs, Observations (n)	Summary of Findings	Consistency and Precision*	Other Limitations	Strength of Evidence*	Applicability
KQ 4 Nonpharmacologic patient-level interventions	k=61 RCTs (39 new) n=7,847	No clear benefit of cognitive stimulation, training, or rehabilitation, exercise interventions, multicomponent interventions, and other interventions on global and domain-specific cognitive function compared with controls at 3 months to 2 years followup among persons with MCI or dementia. Effect estimates generally favored intervention groups, but the magnitude of effects was inconsistent across trials and represented very wide CIs. Measures related to physical function, QOL, and mental and neuropsychiatric symptoms were only reported by half or less of the trials for each intervention group and few found robust differences between groups.	Reasonably consistent Imprecise	Small studies of limited duration. Types of outcomes, specific measures, and duration of followup was highly variable across trials.	Low evidence of small to no benefit	Broad range of older adults with MCI and mild and moderate dementia. Very sparse reporting of clinical characteristics of the included patients such as race/ethnicity and education. Virtually no data on effect modification by important clinical differences. Many complex interventions may not be widely available in the U.S.

Table 22. Summary of Evidence

Key Question Instrument or Treatment	Studies (k) Study Designs, Observations (n)	Summary of Findings	Consistency and Precision*	Other Limitations	Strength of Evidence*	Applicability
KQ 4 Caregiver and caregiver-patient dyad interventions	k=88 RCTs (33 new) n=14,880	Consistent benefit of psychoeducation and care and case management interventions on caregiver burden and depression outcomes. However, effect sizes were mostly small and are of unclear clinical significance. For caregiver burden, the standardized pooled effect was -0.24 (95% CI, -0.36 to -0.13]; I^2=50.2%; k=27; n=2,776) for psychoeducation interventions and -0.54 (95% CI, -0.85 to -0.22); k=8; n=1,215; I^2=82.9%) for care and case management interventions. Other outcomes such as caregiver or patient QOL, rates or time to institutionalization, patient mental health and neuropsychiatric symptoms, and patient functional ability were sparsely reported across the trials with no consistent evidence of a benefit. Decision-making and preparation for meeting dementia-related needs were only reported by one trial each with neither finding statistically significant benefit of the interventions versus control conditions on overall scores for these measures.	Reasonably consistent Precise	Little evidence of longer-term effects; inconsistency in outcomes and specific measures across trials with many providing little data on precise scales used.	Moderate evidence of small benefit	Generally applicable to caregivers of persons with moderate dementia. Many complex interventions may not be widely available in the U.S.
KQ 5 AChEIs and memantine	k=48 RCTs (6 new) n=22,431 k=3 obs. studies (1 new) n=190,076	Side effects from medications were common. Withdrawal or discontinuation was more common with AChEIs (13% withdrawing for donepezil and rivastigmine, 14% for galantamine) than placebo (8%). Memantine appeared to be better tolerated, with no difference in withdrawal rates (8%) compared with placebo (8%). In total, there did not appear to be a difference in total SAEs for these medications across trials with limited duration of followup. However, individual studies, including observational evidence, reported increased rates of bradycardia, and relatedly, of syncope, falls and need for pacemaker placement among those exposed versus unexposed to AChEIs.	Reasonably consistent Precise	The definitions of serious adverse events, which likely vary, were rarely described in the included studies.	Moderate evidence of harm	Mostly represented patients with moderate dementia.

Table 22. Summary of Evidence

Key Question Instrument or Treatment	Studies (k) Study Designs, Observations (n)	Summary of Findings	Consistency and Precision*	Other Limitations	Strength of Evidence*	Applicability
KQ 5 Other medications and supplements	k=21 RCTs (4 new) n=5,688	Across interventions, harms were not clearly significantly increased in intervention vs. control groups.	Reasonably consistent Precise	Small trials often with differential attrition between groups. Lack of consistency in formulations and dosages of agents used.	Low evidence of no harm	Older adults with mild to moderate dementia. Unclear representation of ethnic minorities and those of varying education levels.
KQ 5 Nonpharmacologic patient-level interventions	k=12 RCTs (11 new) n=2,370	Little evidence of harms from good quality studies. Evidence of greater musculoskeletal problems among persons taking part in exercise interventions versus comparators. One trial reported one case of atrial fibrillation among one patient during an exercise session.	Reasonably consistent Precise	Sparse reporting of harms. Trials of exercise interventions more likely to report monitoring harms than cognitive training or other interventions	Low evidence of no harm†	Applicable to patients with mild-to-moderate dementia and MCI.
KQ 5 Caregiver and caregiver-patient dyad interventions	k=4 RCTs (3 new) n=486	No harms evident.	NA	Sparse reporting of harms for patients or caregivers.	Low evidence of no harm†	Generally applicable to caregivers of persons with moderate dementia.

* For KQ 4, consistency, precision, and strength of evidence, assessments were based on primary outcomes within each body of evidence. For AChEIs and memantine, assessments were for cognitive function and global function outcomes. For, other medications and supplements assessments were for cognitive function. For nonpharmacologic patient-level interventions, assessments were for cognitive function, physical function, and neuropsychiatric symptoms. For caregiver and caregiver-patient dyad interventions, assessments were for caregiver burden and depression outcomes.

† No hypothesized serious harms of nonpharmacologic patient or caregiver interventions. Thus, despite few trials reporting this outcome, we have low confidence that the finding of no harm in these two trials reflects this body of evidence.

Abbreviations: AChEIs = acetylcholinesterase inhibitors AD = Alzheimer's disease; CI = confidence interval; CIBIC+ = Clinicians' Interview-Based Impression of Change plus informant input; CG = control group; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-CoA reductase; IG = intervention group; K = number of trials; MCI = mild cognitive impairment; N = population size; n = sample size; NA = not applicable; NR = not reported; NSAIDs = Nonsteroidal Anti-inflammatory Drugs; obs = observational; RCT = randomized controlled trial; SAE = serious adverse events; vs = versus

Table 23. Positive and Negative Predictive Values for Various Sensitivity and Specificity Values, by Age Group

	Age Group, years	Dementia prevalence, percent*	PPV, percent	NPV, percent
Sensitivity 70 Specificity 80	65-74	3	10	99
	75-84	10	28	96
	85+	30	60	86
Sensitivity 80 Specificity 90	65-74	3	20	99
	75-84	10	47	98
	85+	30	77	91
Sensitivity 90 Specificity 90	65-74	3	22	100
	75-84	10	50	99
	85+	30	79	95

* Dementia prevalence based on 2012 data reported by Langa and colleagues.[23]

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

Appendix A. Literature Search Strategies

Key:
/ = MeSH subject heading
* = truncation
* preceding a word = major focus
$ = truncationLL
ab = word in abstract
exp = explode
fs = MeSH subheading
hw = subject heading word
id = identifier
kf = keyword heading [word not phrase indexed]

kw = keyword
md = methodology
mp = mapping alias (searches within: Title (TI), Abstract (AB), Subject Headings Word (HW), Table of Contents Titles/Headings (TC), Original Title (OT), Test & Measures (TM), and Key Phrase Identifiers (ID) fields)
pt = publication type
ti = word in title

Cochrane Central Register of Controlled Trials (CENTRAL)

#1	dementia:ti,kw or alzheimer*:kw
#2	(cognitive next impairment*):ti,kw
#3	(cognitive next decline):ti,kw
#4	(cognitive next loss):ti,kw
#5	(cognitive next disorder*):ti,kw
#6	(cognition next disorder*):ti,kw
#7	446-#6
#8	(screen* or instrument or instruments):ti,ab,kw
#9	(assess* or tool* or test* or evaluat* or questionnaire*):ti,kw
#10	#8 or #9
#11	#7 and #10
#12	(sensitivit* or specificit*):ti,ab,kw
#13	"ROC Curve":ti,ab,kw
#14	"predictive value":ti,ab,kw
#15	accuracy:ti,ab,kw
#16	(False next Negative*):ti,ab,kw
#17	(False next positive*):ti,ab,kw
#18	(Diagnostic next Error*):ti,ab,kw
#19	Reproducibility:ti,ab,kw
#20	(Reference next Value*):ti,ab,kw
#21	(Reference next standard*):ti,ab,kw
#22	(Observer next Variation*):ti,ab,kw
#23	{or #12-#22}

#24 #7 and #23

#25 statin*:ti,ab,kw

#26 (antihypertensive* or diuretic* or (beta next blocker*) or (alpha next blocker*) or (ace next inhibitor*) or "calcium channel" or vasodilator*):ti,ab,kw

#27 (nsaid* or nonsteroidal):ti,ab,kw

#28 aspirin:ti,ab,kw

#29 (hormone* or estrogen* or estradiol or Medroxyprogesterone or Progesterone or androgen* or testosterone or Dehydroepiandrosterone or Norethindrone):ti,ab,kw

#30 (cholinesterase or donepezil or galantamine):ti,ab,kw

#31 memantine:ti,ab,kw

#32 (folic or folate or "vitamin b" or bl or b2 or b6 or b12):ti,ab,kw

#33 (antioxidant* or "vitamin e" or "ascorbic acid" or ascorbate or "vitamin c" or "beta carotene"):ti,ab,kw

#34 (omega* or "fatty acid" or "fatty acids" or linolenic or "mediterranean diet"):ti,ab,kw

#35 (exercis* or "physical activity" or "physical training" or "strength training" or "resistance training" or "aerobic training" or "cardiovascular training" or "endurance training" or "flexibility training" or relaxation or walking or yoga or "tai chi" or danc*):ti,ab,kw

#36 (caregiv* or carer* or "self help" or "family therapy" or "social support" or "skills training" or education):ti,ab,kw

#37 (counsel* or psychotherapy or (behavio* next therap*) or (cognitive next therap*)):ti,ab,kw

#38 (engage* or "cognitive exercise" or "cognitive exercises"):ti,ab,kw

#39 ("case management" or "care management"):ti,ab,kw

#40 (multicomponent or multidisciplinary or multimodal):ti,ab,kw

#41 ("multi component" or "multi disciplinary" or "multi modal"):ti,ab,kw

#42 {or #25-#41}

#43 #7 and #42

#44 #11 or #24 or #43 Publication Year from 2012 to 2017

Dementia/Mild cognitive impairment

Screening trials

Ovid Medline, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily Update

1 Dementia/

2 Alzheimer Disease/

3 Dementia, Vascular/

4 Dementia, Multi-Infarct/

5 Frontotemporal Lobar Degeneration/

Appendix A. Literature Search Strategies

6 Lewy Body Disease/

7 dementia.ti.

8 Neurocognitive Disorders/

9 Cognition Disorders/

10 Cognitive Dysfunction/

11 cognitive impairment*.ti.

12 cognitive decline.ti.

13 cognitive loss.ti.

14 cognitive disorder*.ti.

15 cognitive dysfunction*.ti.

16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17 Mass screening/

18 screen*.ti,ab.

19 17 or 18

20 16 and 19

21 *Dementia/di

22 *Alzheimer Disease/di

23 *Neurocognitive Disorders/di

24 *Cognition Disorders/di

25 *Cognitive Dysfunction/di

26 20 or 21 or 22 or 23 or 24 or 25

27 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/

28 meta-analysis as topic/ (17142)

29 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or pragmatic clinical trial).pt.

30 random*.ti,ab.

31 control groups/ or double-blind method/ or single-blind method/ (184630)

32 clinical trial*.ti,ab.

33 controlled trial*.ti,ab.

34 (metaanaly* or meta analy*).ti,ab.

35 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

36 26 and 35

37 Animals/ not (Humans/ and Animals/)

38 36 not 37

39 limit 38 to (english language and yr="2012 -Current")

40 remove duplicates from 39

Dementia/Mild cognitive impairment

Test performance of screening instruments

Ovid Medline, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily Update

1 Dementia/
2 Alzheimer Disease/
3 Dementia, Vascular/
4 Dementia, Multi-Infarct/
5 Frontotemporal Lobar Degeneration/
6 Lewy Body Disease/
7 dementia.ti.
8 Neurocognitive Disorders/
9 Cognition Disorders/
10 Cognitive Dysfunction/
11 cognitive impairment*.ti.
12 cognitive decline.ti.
13 cognitive loss.ti.
14 cognitive disorder*.ti.
15 cognitive dysfunction*.ti.
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 Mass screening/
18 neuropsychological tests/ or mental navigation tests/
19 (screen* or instrument or instruments).ti,ab.
20 (assess* or tool* or test* or evaluat* or questionnaire*).ti,kf.
21 17 or 18 or 19 or 20
22 "Sensitivity and Specificity"/
23 "Predictive Value of Tests"/
24 ROC Curve/
25 Receiver operat*.ti,ab.
26 (sensitivit* or specificit*).ti,ab.
27 predictive value.ti,ab.
28 accuracy.ti,ab.
29 False Negative Reactions/
30 False Positive Reactions/

31 Diagnostic Errors/

32 "Reproducibility of Results"/

33 Reference Values/

34 Reference Standards/

35 Observer Variation/

36 Psychometrics/

37 Psychometric$.ti,ab.

38 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37

39 16 and 21 and 38

40 Animals/ not (Humans/ and Animals/)

41 39 not 40

42 limit 41 to (english language and yr="2012 -Current")

43 remove duplicates from 42

Dementia/Mild cognitive impairment

Screening harms

Ovid Medline, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily Update

1 Dementia/

2 Alzheimer Disease/

3 Dementia, Vascular/

4 Dementia, Multi-Infarct/

5 Frontotemporal Lobar Degeneration/

6 Lewy Body Disease/

7 dementia.ti.

8 Neurocognitive Disorders/

9 Cognition Disorders/

10 Cognitive Dysfunction/

11 cognitive impairment*.ti.

12 cognitive decline.ti.

13 cognitive loss.ti.

14 cognitive disorder*.ti.

15 cognitive dysfunction*.ti.

16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17 Mass screening/

18 screen*.ti,ab.

19 17 or 18

20 16 and 19

21 *Dementia/di

22 *Alzheimer Disease/di

23 *Neurocognitive Disorders/di

24 *Cognition Disorders/di

25 *Cognitive Dysfunction/di

26 20 or 21 or 22 or 23 or 24 or 25

27 adverse effects.fs.

28 adverse*.ti,ab.

29 harm*.ti,ab.

30 Anxiety/

31 anxiety.ti,ab.

32 Depression/

33 depression.ti,ab.

34 Depressive Disorder/

35 labeling.ti,ab.

36 labelling.ti,ab.

37 labeled.ti,ab.

38 labelled.ti,ab.

39 Stress, Psychological/

40 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39

41 26 and 40

42 Animals/ not (Humans/ and Animals/)

43 41 not 42

44 limit 43 to (english language and yr="2012 -Current")

45 remove duplicates from 44

Dementia/Mild cognitive impairment

Treatment trials

Ovid Medline, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily Update

1 Dementia/

2 Alzheimer Disease/

3 Dementia, Vascular/

4 Dementia, Multi-Infarct/

Appendix A. Literature Search Strategies

5 Frontotemporal Lobar Degeneration/

6 Lewy Body Disease/

7 dementia.ti.

8 Neurocognitive Disorders/

9 Cognition Disorders/

10 Cognitive Dysfunction/

11 cognitive impairment*.ti.

12 cognitive decline.ti.

13 cognitive loss.ti.

14 cognitive disorder*.ti.

15 cognitive dysfunction*.ti.

16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17 Hydroxymethylglutaryl-CoA Reductase Inhibitors/

18 statin*.mp.

19 lovastatin.mp.

20 simvastatin.mp.

21 cerivastatin.mp.

22 atorvastatin.mp.

23 rosuvastatin.mp.

24 pravastatin.mp.

25 fluvastatin.mp.

26 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25

27 Antihypertensive Agents/

28 Antihypertensive*.ti,ab.

29 Diuretics/

30 Diuretic*.ti,ab.

31 exp Adrenergic beta-Antagonists/

32 Adrenergic beta Antagonist*.ti,ab.

33 beta blocker*.ti,ab.

34 exp Adrenergic alpha-Antagonists/

35 Adrenergic alpha Antagonist*.ti,ab.

36 alpha blocker*.ti,ab.

37 Angiotensin-Converting Enzyme Inhibitors/

38 ace inhibitor*.ti,ab.

39 Angiotensin Converting Enzyme Inhibitor*.ti,ab.

40 Calcium Channel Blockers/
41 Calcium Channel Blocker*.ti,ab.
42 Vasodilator Agents/
43 Vasodilator*.ti,ab.
44 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45 Aspirin/
46 aspirin*.ti,ab.
47 45 or 46
48 Anti-Inflammatory Agents, Non-Steroidal/
49 Nonsteroidal Anti Inflammatory Agent*.ti,ab.
50 Non steroidal Anti Inflammatory Agent*.ti,ab.
51 Nonsteroidal Antiinflammatory Agent*.ti,ab.
52 Non steroidal Antiinflammatory Agent*.ti,ab.
53 NSAID*.ti,ab.
54 Diclofenac/
55 Diclofenac.ti,ab.
56 Ibuprofen/
57 Ibuprofen.ti,ab.
58 Indomethacin/
59 Indomethacin.ti,ab.
60 Ketoprofen/
61 Ketoprofen.ti,ab.
62 Ketorolac/
63 Ketorolac.ti,ab.
64 Naproxen/
65 Naproxen.ti,ab.
66 Piroxicam/
67 Piroxicam.ti,ab.
68 Salicylates/
69 Salicylate*.ti,ab.
70 Sulindac/
71 Sulindac.ti,ab.
72 Cyclooxygenase Inhibitors/
73 Cyclooxygenase Inhibitor*.ti,ab.
74 Cyclooxygenase 2 Inhibitors/

75 Cyclooxygenase 2 Inhibitor*.ti,ab.

76 COX 2 Inhibitor*.ti,ab.

77 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76

78 Gonadal Steroid Hormones/

79 Hormone Replacement Therapy/

80 Estrogen Replacement Therapy/

81 Estradiol/

82 Estrogens/

83 "Estrogens, Conjugated (USP)"/

84 Medroxyprogesterone Acetate/

85 Progesterone/

86 Progesterone Congeners/

87 Androgens/

88 Testosterone/

89 Dehydroepiandrosterone/

90 Dehydroepiandrosterone Sulfate/

91 Norethindrone/

92 Hormone Replacement Therapy.ti,ab.

93 estrogen*.ti,ab.

94 Estradiol.ti,ab.

95 Medroxyprogesterone.ti,ab.

96 Progesterone.ti,ab.

97 Androgen*.ti,ab.

98 Testosterone.ti,ab.

99 Dehydroepiandrosterone.ti,ab.

100 Norethindrone.ti,ab.

101 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 or 98 or 99 or 100

102 Cholinesterase inhibitors/

103 Cholinesterase Inhibitor*.ti,ab.

104 Anticholinesterase*.ti,ab.

105 Galantamine/

106 Galantamine.ti,ab.

107 rivastigmine.ti,ab.

108 donepezil.ti,ab.
109 102 or 103 or 104 or 105 or 106 or 107 or 108
110 Memantine/
111 Memantine.ti,ab.
112 110 or 111
113 folic acid/
114 folic acid.ti,ab.
115 folate.ti,ab.
116 Vitamin B Complex/
117 Thiamine/
118 Thiamine.ti,ab.
119 Thiamin.ti,ab.
120 Thiamine Monophosphate/
121 Thiamine Pyrophosphate/
122 Thiamine Triphosphate/
123 Vitamin B 1.ti,ab.
124 Vitamin B1.ti,ab.
125 Riboflavin/
126 Riboflavin.ti,ab.
127 Vitamin B 2.ti,ab.
128 Vitamin B2.ti,ab.
129 Vitamin B 6/
130 Vitamin B 6.ti,ab.
131 Vitamin B6.ti,ab.
132 Pyridoxine/
133 Pyridoxine.ti,ab.
134 Vitamin B 12/
135 Vitamin B 12.ti,ab.
136 Vitamin B12.ti,ab.
137 Cobamides/
138 Hydroxocobalamin/
139 Cobalamin.ti,ab.
140 Cyanocobalamin.ti,ab.
141 Cobamides.ti,ab.
142 Hydroxocobalamin.ti,ab.

143 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142
144 Antioxidants/
145 Antioxidant*.ti,ab.
146 Vitamin E/
147 Vitamin E.ti,ab.
148 alpha-Tocopherol/
149 Tocopherols/
150 Tocopherol*.ti,ab.
151 Ascorbic acid/
152 Ascorbic acid.ti,ab.
153 Vitamin C.ti,ab.
154 ascorbate.ti,ab.
155 beta carotene/
156 beta carotene.ti,ab.
157 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156
158 fatty acids, omega-3/ or alpha-linolenic acid/ or docosahexaenoic acids/ or neuroprostanes/ or eicosapentaenoic acid/
159 Omega 3.ti,ab.
160 n 3 Fatty Acid*.ti,ab.
161 Linolenic Acids/
162 Linolenic Acid*.ti,ab.
163 Fatty Acids, Essential/
164 Dietary Fats, Unsaturated/
165 Fish Oils/
166 fish oil*.ti,ab.
167 diet* fatty acid*.ti,ab.
168 Diet, Mediterranean/
169 Mediterranean diet*.ti,ab.
170 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169
171 Exercise/
172 Exercise Therapy/
173 Exercise Movement Techniques/
174 Physical Fitness/
175 Cardiorespiratory Fitness/

176 Physical Conditioning, Human/
177 Walking/
178 Stair Climbing/
179 Circuit-Based Exercise/
180 Resistance Training/
181 exercis*.ti,ab.
182 physical activity.ti,ab.
183 physical training.ti,ab.
184 strength training.ti,ab.
185 resistance training.ti,ab.
186 aerobic training.ti,ab.
187 cardiovascular training.ti,ab.
188 endurance training.ti,ab.
189 flexibility training.ti,ab.
190 Relaxation/
191 Relaxation Therapy/
192 relaxation.ti,ab.
193 Tai Ji/
194 Tai Chi.ti,ab.
195 walking.ti,ab.
196 Yoga/
197 yoga.ti,ab.
198 Dancing/
199 (dancing or dance).ti,ab.
200 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 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 Caregivers/
202 caregiver*.ti,ab.
203 caregiving.ti,ab.
204 (carer or carers).ti,ab.
205 Self-Help Groups/
206 self help.ti,ab.
207 care giver*.ti,ab.
208 Family Therapy/
209 family therapy.ti,ab.

210 Social Support/

211 social support*.ti,ab.

212 skills training.ti,ab.

213 Health Education/

214 health education.ti,ab.

215 education.fs.

216 education, continuing/ or education, medical, continuing/ or education, nursing, continuing/

217 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216

218 Counseling/

219 Directive Counseling/

220 Cognitive Therapy/

221 cognitive therap*.ti,ab.

222 psychotherapy/ or psychotherapy, brief/

223 Behavior Therapy/

224 behavio* therap*.ti,ab.

225 psychotherap*.ti,ab.

226 counsel*.ti,ab.

227 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226

228 (cognitive* adj3 engage*).ti,ab.

229 (creative* adj3 engage*).ti,ab.

230 (cognitive* adj3 stimulat*).ti,ab.

231 cognitive training.ti,ab.

232 cognitive intervention*.ti,ab.

233 group reminiscence.ti,ab.

234 reality orientation.ti,ab.

235 Reality Therapy/

236 reality therapy.ti,ab.

237 cognitive exercis*.ti,ab.

238 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237

239 Case Management/

240 Patient Care Management/

241 care manage*.ti,ab.

242 case manage*.ti,ab.

243 239 or 240 or 241 or 242

244 ((multicomponent or multi component or multidisciplinary or multi disciplinary or multimodal or multi modal)

adj3 (treatment* or program* or intervention*)).ti,ab.

245 26 or 44 or 47 or 77 or 101 or 109 or 112 or 143 or 157 or 170 or 200 or 217 or 227 or 238 or 243 or 244

246 16 and 245

247 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/

248 meta-analysis as topic/

249 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or pragmatic clinical trial).pt.

250 random*.ti,ab.

251 control groups/ or double-blind method/ or single-blind method/

252 clinical trial*.ti,ab.

253 controlled trial*.ti,ab.

254 (metaanaly* or meta analy*).ti,ab.

255 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254

256 246 and 255

257 Animals/ not (Humans/ and Animals/)

258 256 not 257

259 limit 258 to (english language and yr="2012 -Current")

260 remove duplicates from 259

Dementia/Mild cognitive impairment

Treatment harms

Ovid Medline, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily Update

1 Dementia/

2 Alzheimer Disease/

3 Dementia, Vascular/

4 Dementia, Multi-Infarct/

5 Frontotemporal Lobar Degeneration/

6 Lewy Body Disease/

7 dementia.ti.

8 Neurocognitive Disorders/

9 Cognition Disorders/

10 Cognitive Dysfunction/

11 cognitive impairment*.ti.

12 cognitive decline.ti.

13 cognitive loss.ti.

14 cognitive disorder*.ti.
15 cognitive dysfunction*.ti.
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 Hydroxymethylglutaryl-CoA Reductase Inhibitors/
18 statin*.mp.
19 lovastatin.mp.
20 simvastatin.mp.
21 cerivastatin.mp.
22 atorvastatin.mp.
23 rosuvastatin.mp.
24 pravastatin.mp.
25 fluvastatin.mp.
26 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27 Antihypertensive Agents/
28 Antihypertensive*.ti,ab.
29 Diuretics/
30 Diuretic*.ti,ab.
31 exp Adrenergic beta-Antagonists/
32 Adrenergic beta Antagonist*.ti,ab.
33 beta blocker*.ti,ab.
34 exp Adrenergic alpha-Antagonists/
35 Adrenergic alpha Antagonist*.ti,ab.
36 alpha blocker*.ti,ab.
37 Angiotensin-Converting Enzyme Inhibitors/
38 ace inhibitor*.ti,ab.
39 Angiotensin Converting Enzyme Inhibitor*.ti,ab.
40 Calcium Channel Blockers/
41 Calcium Channel Blocker*.ti,ab.
42 Vasodilator Agents/
43 Vasodilator*.ti,ab.
44 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45 Aspirin/
46 aspirin*.ti,ab.
47 45 or 46
48 Anti-Inflammatory Agents, Non-Steroidal/

49 Nonsteroidal Anti Inflammatory Agent*.ti,ab.
50 Non steroidal Anti Inflammatory Agent*.ti,ab.
51 Nonsteroidal Antiinflammatory Agent*.ti,ab.
52 Non steroidal Antiinflammatory Agent*.ti,ab.
53 NSAID*.ti,ab.
54 Diclofenac/
55 Diclofenac.ti,ab.
56 Ibuprofen/
57 Ibuprofen.ti,ab.
58 Indomethacin/
59 Indomethacin.ti,ab.
60 Ketoprofen/
61 Ketoprofen.ti,ab.
62 Ketorolac/
63 Ketorolac.ti,ab.
64 Naproxen/
65 Naproxen.ti,ab.
66 Piroxicam/
67 Piroxicam.ti,ab.
68 Salicylates/
69 Salicylate*.ti,ab.
70 Sulindac/
71 Sulindac.ti,ab.
72 Cyclooxygenase Inhibitors/
73 Cyclooxygenase Inhibitor*.ti,ab.
74 Cyclooxygenase 2 Inhibitors/
75 Cyclooxygenase 2 Inhibitor*.ti,ab.
76 COX 2 Inhibitor*.ti,ab.
77 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76
78 Gonadal Steroid Hormones/
79 Hormone Replacement Therapy/
80 Estrogen Replacement Therapy/
81 Estradiol/
82 Estrogens/

83 "Estrogens, Conjugated (USP)"/

84 Medroxyprogesterone Acetate/

85 Progesterone/

86 Progesterone Congeners/

87 Androgens/

88 Testosterone/

89 Dehydroepiandrosterone/

90 Dehydroepiandrosterone Sulfate/

91 Norethindrone/

92 Hormone Replacement Therapy.ti,ab.

93 estrogen*.ti,ab.

94 Estradiol.ti,ab.

95 Medroxyprogesterone.ti,ab.

96 Progesterone.ti,ab.

97 Androgen*.ti,ab.

98 Testosterone.ti,ab.

99 Dehydroepiandrosterone.ti,ab.

100 Norethindrone.ti,ab.

101 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 or 98 or 99 or 100

102 Cholinesterase inhibitors/

103 Cholinesterase Inhibitor*.ti,ab.

104 Anticholinesterase*.ti,ab.

105 Galantamine/

106 Galantamine.ti,ab.

107 rivastigmine.ti,ab.

108 donepezil.ti,ab.

109 102 or 103 or 104 or 105 or 106 or 107 or 108

110 Memantine/

111 Memantine.ti,ab.

112 110 or 111

113 folic acid/

114 folic acid.ti,ab.

115 folate.ti,ab.

116 Vitamin B Complex/

117 Thiamine/

118 Thiamine.ti,ab.

119 Thiamin.ti,ab.

120 Thiamine Monophosphate/

121 Thiamine Pyrophosphate/

122 Thiamine Triphosphate/

123 Vitamin B 1.ti,ab.

124 Vitamin B1.ti,ab.

125 Riboflavin/

126 Riboflavin.ti,ab.

127 Vitamin B 2.ti,ab.

128 Vitamin B2.ti,ab.

129 Vitamin B 6/

130 Vitamin B 6.ti,ab.

131 Vitamin B6.ti,ab.

132 Pyridoxine/

133 Pyridoxine.ti,ab.

134 Vitamin B 12/

135 Vitamin B 12.ti,ab.

136 Vitamin B12.ti,ab.

137 Cobamides/

138 Hydroxocobalamin/

139 Cobalamin.ti,ab.

140 Cyanocobalamin.ti,ab.

141 Cobamides.ti,ab.

142 Hydroxocobalamin.ti,ab.

143 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142

144 Antioxidants/

145 Antioxidant*.ti,ab.

146 Vitamin E/

147 Vitamin E.ti,ab.

148 alpha-Tocopherol/

149 Tocopherols/

150 Tocopherol*.ti,ab.

151 Ascorbic acid/

152 Ascorbic acid.ti,ab.

153 Vitamin C.ti,ab.

154 ascorbate.ti,ab.

155 beta carotene/

156 beta carotene.ti,ab.

157 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156

158 fatty acids, omega-3/ or alpha-linolenic acid/ or docosahexaenoic acids/ or neuroprostanes/ or eicosapentaenoic acid/

159 Omega 3.ti,ab.

160 n 3 Fatty Acid*.ti,ab.

161 Linolenic Acids/

162 Linolenic Acid*.ti,ab.

163 Fatty Acids, Essential/

164 Dietary Fats, Unsaturated/

165 Fish Oils/

166 fish oil*.ti,ab.

167 diet* fatty acid*.ti,ab.

168 Diet, Mediterranean/

169 Mediterranean diet*.ti,ab.

170 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169

171 Exercise/

172 Exercise Therapy/

173 Exercise Movement Techniques/

174 Physical Fitness/

175 Cardiorespiratory Fitness/

176 Physical Conditioning, Human/

177 Walking/

178 Stair Climbing/

179 Circuit-Based Exercise/

180 Resistance Training/

181 exercis*.ti,ab.

182 physical activity.ti,ab.

183 physical training.ti,ab.

184 strength training.ti,ab.

185 resistance training.ti,ab.
186 aerobic training.ti,ab.
187 cardiovascular training.ti,ab.
188 endurance training.ti,ab.
189 flexibility training.ti,ab.
190 Relaxation/
191 Relaxation Therapy/
192 relaxation.ti,ab.
193 Tai Ji/
194 Tai Chi.ti,ab.
195 walking.ti,ab.
196 Yoga/
197 yoga.ti,ab.
198 Dancing/
199 (dancing or dance).ti,ab.
200 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 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 Caregivers/
202 caregiver*.ti,ab.
203 caregiving.ti,ab.
204 (carer or carers).ti,ab.
205 Self-Help Groups/
206 self help.ti,ab.
207 care giver*.ti,ab.
208 Family Therapy/
209 family therapy.ti,ab.
210 Social Support/
211 social support*.ti,ab.
212 skills training.ti,ab.
213 Health Education/
214 health education.ti,ab.
215 education.fs.
216 education, continuing/ or education, medical, continuing/ or education, nursing, continuing/
217 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216
218 Counseling/

219 Directive Counseling/
220 Cognitive Therapy/
221 cognitive therap*.ti,ab.
222 psychotherapy/ or psychotherapy, brief/
223 Behavior Therapy/
224 behavio* therap*.ti,ab.
225 psychotherap*.ti,ab.
226 counsel*.ti,ab.
227 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226
228 (cognitive* adj3 engage*).ti,ab.
229 (creative* adj3 engage*).ti,ab.
230 (cognitive* adj3 stimulat*).ti,ab.
231 cognitive training.ti,ab.
232 cognitive intervention*.ti,ab.
233 group reminiscence.ti,ab.
234 reality orientation.ti,ab.
235 Reality Therapy/
236 reality therapy.ti,ab.
237 cognitive exercis*.ti,ab.
238 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237
239 Case Management/
240 Patient Care Management/
241 care manage*.ti,ab.
242 case manage*.ti,ab.
243 239 or 240 or 241 or 242
244 ((multicomponent or multi component or multidisciplinary or multi disciplinary or multimodal or multi modal) adj3 (treatment* or program* or intervention*)).ti,ab.
245 26 or 44 or 47 or 77 or 101 or 109 or 112 or 143 or 157 or 170 or 200 or 217 or 227 or 238 or 243 or 244
246 16 and 245
247 safety/
248 safety.ti,ab.
249 adverse event*.ti,ab.
250 adverse effects.fs.
251 adverse effect*.ti,ab.
252 adverse outcome*.ti,ab.

253 side effect*.ti,ab.
254 product surveillance, postmarketing/
255 "Drug-Related Side Effects and Adverse Reactions"/
256 Long Term Adverse Effects/
257 Adverse reaction*.ti,ab.
258 Adverse drug reaction*.ti,ab.
259 drug toxicity/
260 drug toxicity.ti,ab.
261 Harm*.ti,ab.
262 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261
263 case-control studies/
264 retrospective studies/
265 cohort studies/
266 longitudinal studies/
267 follow-up studies/
268 prospective studies/
269 Cross-Sectional Studies/
270 cohort.ti,ab.
271 longitudinal.ti,ab.
272 follow up.ti,ab.
273 followup.ti,ab.
274 prospective*.ti,ab.
275 retrospective*.ti,ab.
276 comparison group*.ti,ab.
277 control group*.ti,ab.
278 observational.ti,ab.
279 nonrandom*.ti,ab.
280 database*.ti,ab.
281 population*.ti,ab.
282 cross sectional.ti,ab.
283 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282
284 246 and 262 and 283
285 Animals/ not (Humans/ and Animals/)
286 284 not 285

287 limit 286 to (english language and yr="2012 -Current")

288 remove duplicates from 287

Dementia/Mild cognitive impairment

Screening

PsycInfo

1 Dementia/

2 Dementia with Lewy bodies/

3 Senile Dementia/

4 Vascular Dementia/

5 Alzheimer's Disease/

6 Cognitive Impairment/

7 cognitive impairment$.ti.

8 cognitive decline.ti.

9 cognitive loss.ti.

10 cognitive disorder$.ti.

11 or/1-10

12 Screening/

13 Health Screening/

14 Screening Tests/

15 (screen$ or instrument or instruments).ti,ab,id.

16 12 or 13 or 14 or 15

17 11 and 16

18 treatment outcome.md.

19 experiment controls/

20 controlled trial$.ti,ab,id,hw.

21 clinical trial$.ti,ab,id,hw.

22 random$.ti,ab,id,hw.

23 placebo$.ti,ab,id,hw.

24 meta analy$.ti,ab,hw,id.

25 metaanaly$.ti,ab,hw,id.

26 or/18-25 (238994)

27 Psychometrics/

28 Test Validity/

29 Interrater Reliability/

30 validity.ti,ab,id.
31 reliability.ti,ab,id.
32 psychometrics.ti,ab,id.
33 Receiver operat$.ti,ab,id.
34 ROC curve$.ti,ab,id.
35 sensitivit$.ti,ab,id.
36 specificit$.ti,ab,id.
37 predictive value.ti,ab,id.
38 accuracy.ti,ab,id.
39 false positive$.ti,ab,id.
40 false negative$.ti,ab,id.
41 miss rate$.ti,ab,id.
42 error rate$.ti,ab,id.
43 or/27-42
44 Anxiety/
45 Anxiety Disorders/
46 "Depression (Emotion)"/
47 Labeling/ (2507)
48 Psychological Stress/
49 adverse$.ti,ab,id.
50 harm$.ti,ab,id.
51 anxiety.ti,ab,id.
52 depression.ti,ab,id.
53 (labeling or labelling or labeled or labelled).ti,ab,id.
54 or/44-53
55 17 and (26 or 43 or 54)
56 17 and 55
57 limit 56 to (english language and yr="2012 -Current")

Dementia/Mild cognitive impairment

Treatment

PsycInfo

1 Dementia/
2 Dementia with Lewy bodies/
3 Senile Dementia/

4 Vascular Dementia/
5 Alzheimer's Disease/
6 Cognitive Impairment/
7 cognitive impairment$.ti.
8 cognitive decline.ti.
9 cognitive loss.ti.
10 cognitive disorder$.ti.
11 or/1-10
12 (multicomponent$ or multidisciplinary or multimodal or multi component or multi disciplinary or multi modal).mp.
13 (case management or care management).mp.
14 (cognitive training or cognitive intervention$ or counseling or cognitive therapy).mp.
15 (reminiscence or reality therapy).mp.
16 (Cognitive$ adj3 engage$).mp.
17 (behavio$ therap$ or cognitive behavio$ therap$ or psychotherapy).mp.
18 (Caregiv$ or carer).mp.
19 support group$.mp.
20 (self help or family therapy or social support).mp.
21 (health education or continuing education).mp.
22 (exercis$ or physical activity).mp.
23 ((physical or strength or resistance or aerobic or cardiovascular or endurance or flexibility) adj training).mp.
24 (relaxation or tai chi or walking or yoga or dancing or dance).mp.
25 (Caregiv$ or carer).mp.
26 (self help or family therapy or social support or support group*).mp.
27 (health education or continuing education or skills training).mp.
28 (behavio$ therap$ or cognitive behavio$ therap$ or psychotherapy).mp.
29 (cognitive training or cognitive intervention$ or counseling or cognitive therap$).mp.
30 (Cognitive$ adj3 (engage$ or stimulat$)).mp.
31 (creative adj4 engage$).mp.
32 (creative adj3 engage$).mp.
33 (reminiscence or reality therapy or reality orientation).mp.
34 (case management or care management).mp.
35 (multicomponent or multidisciplinary or multimodal or multi component or multi disciplinary or multi modal).mp.
36 or/12-35
37 11 and 36
38 treatment outcome.md.

39 experiment controls/

40 controlled trial$.ti,ab,id,hw.

41 clinical trial$.ti,ab,id,hw.

42 random$.ti,ab,id,hw.

43 placebo$.ti,ab,id,hw.

44 meta analy$.ti,ab,hw,id.

45 metaanaly$.ti,ab,hw,id.

46 or/38-45

47 37 and 46

48 Anxiety/

49 Anxiety Disorders/

50 "Depression (Emotion)"/

51 Psychological Stress/

52 exp "side effects (treatment)"/

53 safety.ti,ab,id.

54 adverse$.ti,ab,id.

55 harm$.ti,ab,id.

56 anxiety.ti,ab,id.

57 depression.ti,ab,id.

58 or/48-57

59 37 and 58

60 47 or 59

61 limit 60 to (english language and yr="2012 -Current")

PubMed, publisher-supplied records

#26 #25 AND English[Language] AND ("2012"[Date - Publication] : "3000"[Date - Publication])

#25 #24 AND publisher[sb]

#24 #5 OR #7 OR #23

#23 #1 AND #22

#22 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21

#21 (exercis*[tiab] OR "physical activity"[tiab] OR "physical training"[tiab] OR "strength training"[tiab] OR "resistance training"[tiab] OR "aerobic training"[tiab] OR "cardiovascular training"[tiab] OR "endurance

training"[tiab] OR "flexibility training"[tiab] OR relaxation[tiab] OR walking[tiab] OR yoga[tiab] OR "tai chi"[tiab] OR danc*[tiab]

#20 multicomponent[tiab] OR multidisciplinary[tiab] OR multimodal[tiab] OR "multi component"[tiab] OR "multi disciplinary"[tiab] OR "multi modal"[tiab]

#19 "case management"[tiab] OR "care management"[tiab]

#18 engage*[tiab] OR "cognitive exercise"[tiab] OR "cognitive exercises"[tiab]

#17 counsel*[tiab] OR psychotherapy[tiab] OR behavio* therap*[tiab] OR cognitive therapy*[tiab]

#16 caregiv*[tiab] OR carer*[tiab] OR "self help"[tiab] OR "family therapy"[tiab] OR "social support"[tiab] OR "skills training"[tiab] OR education[tiab]

#15 omega*[tiab] OR "fatty acid"[tiab] OR "fatty acids"[tiab] OR linolenic[tiab] OR "mediterranean diet"[tiab]

#14 antioxidant*[tiab] OR "vitamin e"[tiab] OR "ascorbic acid"[tiab] OR ascorbate[tiab] OR "vitamin c"[tiab] OR "beta carotene"[tiab]

#13 folic[tiab] OR folate[tiab] OR "vitamin b"[tiab] OR bl[tiab] OR b2[tiab] OR b6[tiab] OR b12[tiab]

#12 cholinesterase[tiab] OR donepezil[tiab] OR galantamine[tiab] OR memantine[tiab]

#11 hormone*[tiab] OR estrogen*[tiab] OR estradiol[tiab] OR Medroxyprogesterone[tiab] OR Progesterone[tiab] OR androgen*[tiab] OR testosterone[tiab] OR Dehydroepiandrosterone[tiab] OR Norethindrone[tiab]

#10 aspirin[tiab]

#9 nsaid*[tiab] OR nonsteroidal[tiab]

#8 statin*[tiab] OR antihypertensive*[tiab] OR diuretic*[tiab] OR beta blocker*[tiab] OR alpha blocker*[tiab] OR ace inhibitor*[tiab] OR "calcium channel"[tiab] OR vasodilator*[tiab]

#7 #1 AND #6

#6 sensitivit*[tiab] OR “ROC Curve”[tiab] OR “predictive value”[tiab] OR accuracy[tiab] OR false negative*[tiab] OR false positive*[tiab] OR diagnostic error*[tiab] OR reproducibility[tiab] OR reference value*[tiab] OR reference value*[tiab] OR reference standard*[tiab] OR observer variation*[tiab]

#5 #3 OR #4

#4 (cognitive[ti] AND screen*[ti])

#3 #1 AND #2

#2 screen*[tiab] OR instrument[tiab] OR instruments[tiab] OR assess*[ti] OR tool*[ti] OR test*[ti] OR evaluat*[ti] OR questionnaire*[ti]

#1 dementia[ti] OR “cognitive impairment”[ti] OR “cognitively impaired”[ti] OR “cognitive impairments”[ti] OR “cognitive loss”[ti] OR “cognitive decline”[ti] OR “cognitive disorder”[ti] OR “cognitive disorders”[ti] OR mci[ti]

Appendix A Table 1. Inclusion and Exclusion Criteria

	Included	Excluded
Condition	**KQs 1–3:** Any cognitive impairment (mild cognitive impairment* or dementia†) **KQs 4, 5:** Mild cognitive impairment* or mild to moderate dementia†	**KQs 4, 5:** Severe dementia
Populations	**KQs 1–3:** Community-dwelling older adults (including those residing in independent living facilities) age ≥65 years (or studies with a mean age ≥65 years) without a current diagnosis of mild cognitive impairment or dementia; informal caregivers taking some responsibility for the care of the patient, such as a spouse, partner, relative, or friend **KQs 4–5:** Community-dwelling older adults (including those residing in independent living facilities) age ≥65 years (or studies with a mean age ≥65 years) with a current diagnosis of mild cognitive impairment or dementia; informal caregivers taking some responsibility for the care of the patient, such as a spouse, partner, relative, or friend	• Studies comprised exclusively of persons diagnosed with depression or psychosis, alcohol use disorder, HIV/AIDS, Down syndrome, posttraumatic brain injury, metabolic disorders, Parkinson's disease, Huntington's disease, or stroke • Persons living in special settings outside of the community (e.g., hospitals, nursing or care homes, rehabilitation centers, other long-term care facilities) • Professional caregivers who are formally or professionally trained and paid a salary
Settings	Primary care outpatient settings (ambulatory care), home, residential care facilities, assisted living facilities, and adult foster care	**All KQs:** Hospitals, intermediate care facilities (e.g., nursing homes, rehabilitation facilities, subacute care facilities), emergency departments, or other settings not generalizable to primary care **KQs 1–3:** Studies in which participants are recruited from memory, dementia, geropsychiatry, or neurology clinics
Screening	Screening instruments that can be delivered in primary care in ≤10 minutes by the clinician or ≤20 minutes by the patient; informant instruments	Screening instruments that take >10 minutes for clinician administration or >20 minutes for self-administration; biomarkers (cerebrospinal fluid, blood plasma, urine) or imaging (computed tomography, magnetic resonance imaging, positron emission tomography)

Interventions	• Use of medications approved by the U.S. Food and Drug Administration (alone or in combination) for the treatment of dementia:
	  ○ Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine)
	  ○ NMDA (N-methyl-D-aspartate) receptor antagonists (memantine)
	• Use of other medications or dietary supplements:
	  ○ Medications aimed at cardiovascular risk reduction for treatment of vascular dementia (antiplatelet medications, antihypertension medications, HMG-CoA reductase inhibitors)
	  ○ Nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, indomethacin, celecoxib)
	  ○ Gonadal steroids (estrogen, progesterone, testosterone)
	  ○ Vitamins, minerals, and antioxidants (B vitamins and folate, vitamins C and E, beta-carotene, omega-3 fatty acids)
		• Treatments for symptom management (e.g., agitation, psychosis, depression) of dementia (i.e., antipsychotics, antiepileptics, antidepressants, selective serotonin reuptake inhibitors)
		• Medications not approved by the U.S. Food and Drug Administration for the treatment of dementia or not available in the United States (e.g., tacrine)
		• Herbal supplements (e.g., ginkgo biloba)
		• Medical foods or fluids or nutrition therapy (e.g., meal replacement therapy)
		• Experimental or emerging therapies (e.g., amyloid disease-modifying treatments)
		• Interventions aimed at noncognitive symptom management (e.g., music, light, pet, reminiscence, or psychodynamic interpersonal therapy; nighttime home monitoring systems; Snoezelen® multisensory environments)
		• Respite care or day care interventions

Appendix A Table 1. Inclusion and Exclusion Criteria

	Included	Excluded
	• Cessation of medications that may be contributing to cognitive impairment (e.g., anticholinergic medications, benzodiazepines) • Nonpharmacologic interventions aimed primarily at the patient, including cognitive training, rehabilitation, or stimulation, with or without motor skills training interventions; exercise interventions; nutrition counseling; multidisciplinary care interventions involving assessment and care coordination; and education-only interventions • Nonpharmacologic interventions aimed primarily at the caregiver or caregiver-patient dyad	
Comparisons	**KQs 1, 3:** No screening, usual care **KQ 2:** Reference standard (clinical assessment or neuropsychologic testing with explicit diagnostic criteria, with or without expert consensus/conference) **KQs 3–5:** • No intervention • Usual care • Wait list • Attention control • Minimal intervention	**KQs 4, 5:** Active intervention
Outcomes	**KQs 1, 4:** *Decisionmaking outcomes:* • For patients and 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; monitored medication use; screening and diagnostic decisions (e.g., cancer screening); and other treatment or management decisions *Patient-related outcomes:* • Health-related quality of life • Incident dementia • Overall dementia severity • Cognitive function • Physical function (e.g., activities of daily living, instrumental activities of daily living) • Global function • Dementia-related symptoms/behaviors (e.g., neuropsychiatric disturbances, insomnia, depression, agitation, verbal aggression, apathy) • Safety (falls, other accidents) • Unanticipated health care utilization (emergency use/hospitalizations) • Institutionalizations/nursing home admissions • Medication adherence/compliance/errors *Family/caregiver-related outcomes:* (a priori defined as primary or secondary outcomes in the trial)	**KQs 1, 4:** *Decisionmaking outcomes:* Cost-related outcomes *Patient-related outcomes:* Cost-related outcomes; patient satisfaction (other than health-related quality of life); biomarker protein levels, brain matter volume, and brain cell activity level; function markers (e.g., Timed Up and Go Test, 6-meter timed walk, Functional Reach Test) *Family/caregiver-related outcomes:* Cost-related outcomes; family/caregiver satisfaction (other than caregiver burden and health-related quality of life) *Societal outcomes:* Cost-related outcomes **KQ 2:** Cost-related outcomes **KQs 3, 5:** Patient or family/caregiver dissatisfaction (other than psychological harms or patient adherence)

Appendix A Table 1. Inclusion and Exclusion Criteria

	Included	Excluded
	• Health-related quality of life • Global stress/distress • Caregiver burden • Depression • Anxiety *Societal outcomes:* Safety (e.g., automobile accidents) **KQ 2:** Sensitivity, specificity, likelihood ratios, positive and negative predictive values, area under the curve **KQ 3:** Paradoxical effects (unwanted or unexpected direction of effects of outcomes), psychological harms (depression, anxiety), and harms due to labeling (psychological harms, insurance status, loss of driving privileges) **KQ 5:** Serious adverse events (e.g., death, serious adverse drug reactions), adverse reactions from medications, unexpected medical attention (e.g., emergency department visits, hospitalizations), paradoxical effects (unwanted or unexpected direction of effects of outcomes), and psychological harms (depression, anxiety)	
Timing of outcome assessment	**KQs 1, 4:** ≥3 months after baseline **KQs 3, 5:** No minimum followup	**KQs 1, 4:** <3 months after baseline
Countries	Studies conducted in countries categorized as "Very High" on the 2014 Human Development Index (as defined by the United Nations Development Programme)	Studies conducted in countries that are not categorized as "Very High" on the 2014 Human Development Index
Study designs	**KQs 1, 4:** Randomized, controlled trials; nonrandomized, controlled trials **KQ 2**: Diagnostic accuracy studies **KQs 3, 5**: Randomized, controlled trials; nonrandomized, controlled trials; open-label extensions of KQ 4 trials; cohort or case-control studies	**KQs 1, 4:** Observational studies **KQ 2**: Case-control studies **KQ 3, 5:** Case series, case reports **KQ 5**: Cohort or case-control studies with <1,000 participants
Publication language	English	Languages other than English
Study quality	Fair- or good-quality studies	Poor-quality studies (according to design-specific USPSTF criteria)

* Mild cognitive impairment is distinguished from dementia by virtue of causing cognitive impairment that is not severe enough to interfere with independence in daily function, although the nomenclature, definitions, and criteria may vary within the included body of evidence.
† Includes major dementia syndromes due to Alzheimer's disease, vascular dementia, frontotemporal dementia, dementia with Lewy bodies, and dementia of mixed etiology.

Abbreviations: KQ = key question; USPSTF = United States Preventive Services Task Force

Appendix A Table 2. Study Design-Specific Quality Rating Criteria*

Study Design	Adapted Quality Criteria
Cohort studies, adapted from Newcastle-Ottawa Scale[109]	**Bias arising in randomization process or due to confounding** • Balance in baseline characteristics • No baseline confounding • No time-varying confounding **Bias in selecting participants into the study** • No evidence of biased selection of sample • Start of followup and start of intervention coincide **Bias due to departures form intended interventions** • Participant intervention status is clearly and explicitly defined and measured • Classification of intervention status is unaffected by knowledge of the outcome or risk of the outcome **Bias in classifying interventions** • Fidelity to intervention protocol • Participants were analyzed as originally allocated **Bias from missing data** • Outcome data are reasonably complete and comparable between groups • Confounding variables that are controlled for in analysis are reasonably complete • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** No evidence that the measures, analyses, or subgroup analyses are selectively reported

Appendix A Table 2. Study Design-Specific Quality Rating Criteria*

Study Design	Adapted Quality Criteria
Diagnostic accuracy studies, adapted from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) I[110] and II[111] instrument	**Patient Selection** • Was a consecutive or random sample of patients enrolled? • Did the study avoid inappropriate exclusions? **Index Test** • Were the index test results interpreted without knowledge of the reference standard results? • If a threshold was used, was it prespecified or was a range of values presented? **Reference Standard** • Is the reference standard likely to correctly classify the target condition? • Were the reference standard results interpreted without knowledge of the index test? • Were staff trained in the use of the reference standard? • Was fidelity of the reference standard monitored or reported? **Flow and Timing** • Was there an appropriate interval between the index test and reference standard? • Did all patients receive a reference standard? • Did all patients receive the same reference standard? ○ Were all patients included in the analysis?
Randomized clinical trials, adapted from U.S. Preventive Services Task Force Manual[108]	**Bias arising in the randomization process or due to confounding** • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias in selecting participants into the study** • CCT only: No evidence of biased selection of sample **Bias due to departures from intended interventions** • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated **Bias from missing data** • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported

* All randomized clinical trials were classified as good, fair, or poor according to the USPSTF Procedure Manual[108]

Appendix A Table 3. Assessment Scales Commonly Used in Included Trials

Domain/Scale	Description	Number of items; range; direction	Clinical Interpretation
Global Cognitive Function	**Memory, orientation, language, praxis, etc.**		
Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog-11)[461, 462]	• Cognitive subscale of the ADAS that includes 11 tasks that include both subject-completed tests and observer-based assessments • Specific tasks include word recall, naming objects and fingers, commands, constructional praxis, ideational praxis, orientation, word recognition, and language • Most sensitive in moderate-stage patients, but not those in mild stage	11; 0–70; higher scores worse	*Interpretation of score:*[462] No impairment: 0 Severe impairment: 70 *Interpretation of change:*[106] A change of 4 points or more on the ADAS-Cog scale is considered a clinically important improvement for mild to moderate dementia
Mini-Mental State Exam (MMSE)[463]	• Clinician administered patient evaluation • Assesses 5 cognitive domains: orientation, memory (registration and recall), attention/calculation, language, and visuospatial abilities	11; 0–30; higher scores better	*Interpretation of score:*[463] No impairment: 30 Severe impairment: 0 *Interpretation of change:*[106] A change of 3 points or more is considered clinically important
Global Function	**Summary outcome assessment of overall severity of condition**		*Any improvement in global function is considered clinical improvement; however, results depend on an individual physician's perception.*
Clinician's Interview-Based Impression of Change with Caregiver Input (CIBIC+)[464]	• Clinician rated (with caregiver input), based on semi-structured interview covering change in cognition, behavior, function	NA (unstructured interview); 1–7; higher scores worse	*Interpretation of score:*[464] Marked improvement: 1 Moderate improvement: 2 Minimal improvement: 3 No change: 4 Minimal worsening: 5 Moderate worsening: 6 Marked worsening: 7
Clinical Dementia Rating (CDR)/CDR-Sum of Boxes (CDR-SB)[465]	• Clinician administered semi-structured interview of patient and a reliable collateral source (e.g., family member) • Characterizes six domains of cognitive functional performance applicable to ADRD: memory, orientation, judgement & problem solving, community affairs, home & hobbies, and personal care	CDR: 6; 0–3; higher scores worse CDR-SB: 6; 0–18; higher scores worse	*Interpretation of score:*[465] CDR: No dementia: 0 Questionable dementia: 0.5 Mild dementia: 1 Moderate dementia: 2 Severe dementia: 3

Appendix A Table 3. Assessment Scales Commonly Used in Included Trials

Domain/Scale	Description	Number of items; range; direction	Clinical Interpretation
Global Deterioration Scale (GDS)[466]	• Clinician rated based on cognitive change only • Provides caregivers an overview of the stages of cognitive function from a primary degenerative dementia such as AD	NA (unstructured interview); 1–7; higher scores worse	*Interpretation of score:*[466] No decline: 1 Very mild cognitive decline: 2 Mild cognitive decline (MCI): 3 Moderate cognitive decline: 4 Moderately severe cognitive decline: 5 Severe cognitive decline: 6 Very severe cognitive decline: 7
Physical Function	**Activities of daily living (ADLs) and Instrumental activities of daily living (IADLs)**		
Alzheimer's Disease Cooperative Study Activities of Daily Living ($ADCS\text{-}ADL_{23}$) (23-item version)[467]	• Informant rated interview developed to evaluate ADL abilities over time and detect changes in patients with mild-to-moderate AD, such as using household appliances, choosing clothes to wear, bathing, and toileting	23; 0–78; higher scores better	*Interpretation of score:*[467] Higher scores indicate less functional impairment
Disability Assessment for Dementia (DAD)[468]	• Administered through an interview with the caregiver/informant • Intended specifically for the assessment of basic ADLs (hygiene, dressing, continence, and eating) and IADLs (meal preparation, telephoning, going on an outing, finance and correspondence, leisure, and housework) in patients with AD. Each activity is evaluated according to three executive factors: initiation, planning-organization, and performance	40; 0–100; higher scores better	*Interpretation of score:*[468] Higher scores indicate less functional disability
Lawton & Brody Instrumental Activities of Daily Living Scale (Lawton IADL)[469]	• Information obtained through self-report or surrogate report • Measures 8 domains of function: ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications, and ability to handle finances	8; 0–8-point scale; higher scores better	*Interpretation of score:*[469] Low function, dependent: 0 High function, independent: 8
Patient Mental Health and Neuropsychiatric Symptoms	**Depression and composite neuropsychiatric symptom scores**		
Cornell Scale for Depression in Dementia (CSDD)[470]	• Information obtained from interview of a caregiver/informant as well as form direct observation and interview of the patient • Designed to assess major depression in elderly people with dementia based on mood-related signs, behavioral disturbance, physical signs, cyclic functions, and ideational disturbance	19; 0–38; higher scores worse	*Interpretation of score:*[470] Absence of significant depression symptoms: <6 Probable depression: ≥10 Definite major depression: ≥18

Appendix A Table 3. Assessment Scales Commonly Used in Included Trials

Domain/Scale	Description	Number of items; range; direction	Clinical Interpretation
Geriatric Depression Scale (GDS)/GDS-15 item (GDS-15)[471]	• Designed to detect depression in the elderly, assessment is based on self-report	GDS: 30; 0–30; higher scores worse GDS-15: 15; 0–15; higher scores worse	*Interpretation of score:* GDS: Normal: 0–9 Mild depression: 10–19 Severe depression: ≥20 GDS-15: Normal: 0–5 Presence of depression (indicates further evaluation needed): 6–10 Definite depression: ≥11
Neuropsychiatric Inventory (NPI-10[472] or NPI-12[473])	• NPI-10: Caregiver/informant interview of 10 behavioral symptom domains rated on a scale based on frequency and severity (delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor behavior) • NPI-12: Caregiver/informant interview of 10 behavioral symptom domains (delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor behavior) and 2 neurovegetative domains (sleep and appetite) rated on a scale based on frequency and severity	NPI-10: 10; 0–120; higher scores worse NPI-12: 12; 0–144; higher scores worse	*Higher scores indicate more behavioral disturbance for both NPI and RMBPC. Unclear interpretation of specific scores.*
Revised Memory and Behavior Problems Checklist (RMBPC) (Total Number of Behavioral and Memory Problems or Total Frequency of Memory and Behavioral Problems)[474]	• Caregiver-administered paper-and-pencil measure • Portion of the RMBPC focused on the frequency and total number of problematic behaviors (memory-related problems, depression, and disruptive behaviors) in patients with dementia	RMBPC (Total): 24; 0–24; higher scores worse RMBPC (Frequency): 24; 0–96; higher scores worse	
Caregiver Depressive Symptomatology			
Center for Epidemiologic Studies – Depression Scale (CES-D)[475]	• Short self-report scale designed to measure depressive symptomatology in caregivers • Scores represent depressed affect, absence of positive affect or anhedonia, somatic activity or inactivity, and interpersonal challenges	20; 0–60; higher scores worse	*Interpretation of score:*[352, 475] Clinically significant depression: ≥16
Beck Depression Inventory (BDI-I, II)[476]	• Self-rated scale that evaluates key symptoms of depression including mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal,	21; 0–63; higher scores worse	*Interpretation of score:* Minimal depression: 0–13 Mild depression: 14–19 Moderate depression: 20–28 Severe depression: 29–63

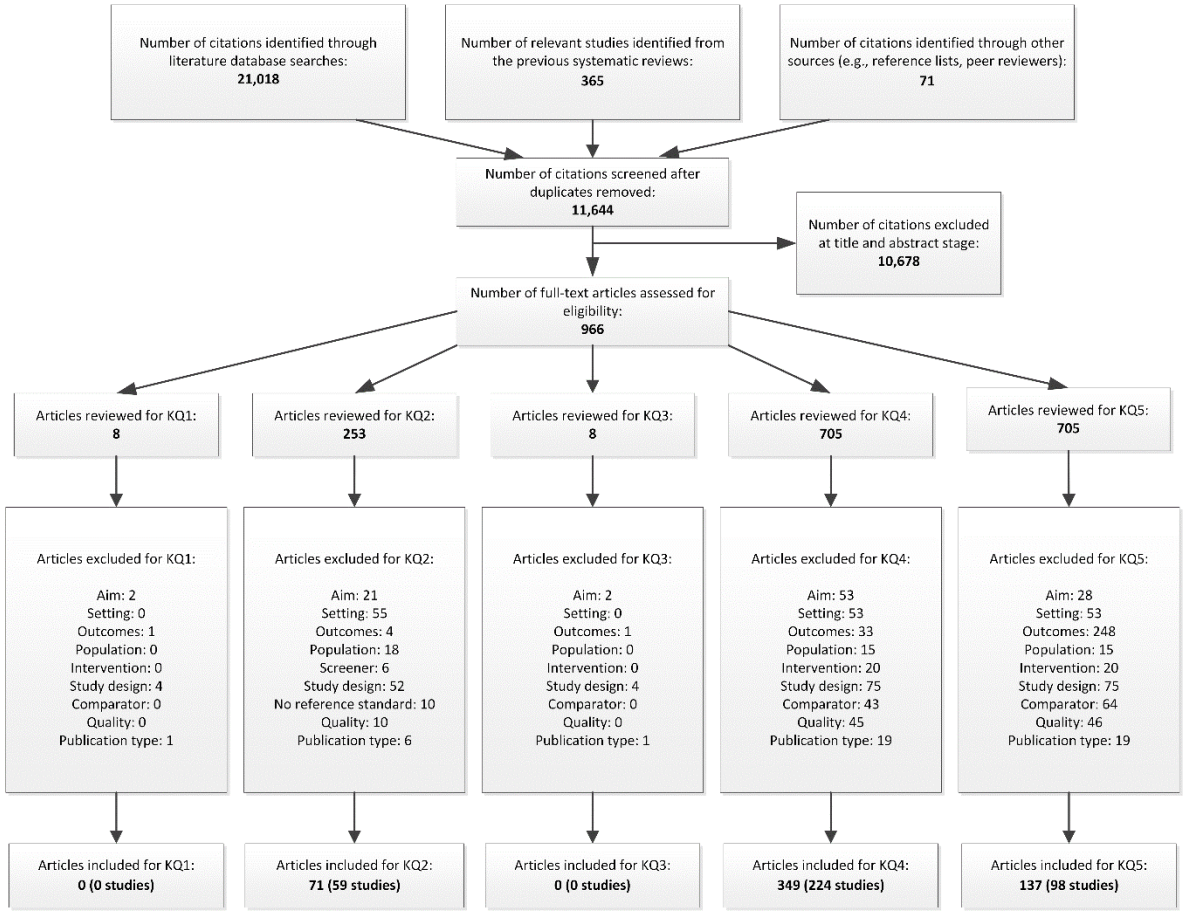
Appendix A Table 3. Assessment Scales Commonly Used in Included Trials

Domain/Scale	Description	Number of items; range; direction	Clinical Interpretation
	indecisiveness, body image change, work difficulty, insomnia, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido		
Caregiver Burden			
Zarit Burden Interview-22 item (Zarit-22)[477]	• Caregiver-rated or clinician-administered interview • Measures perceived social, physical, financial, and emotional burden of caregiving	22; 0–88; higher scores worse	*Higher scores indicate greater caregiver burden for Zarit-22 and RMBPC. Unclear interpretation of specific scores.*
Revised Memory and Behavior Problems Checklist (RMBPC) – Total caregiver reaction to problem behaviors[474]	• Caregiver-administered paper-and-pencil measure • Portion of the RMBPC focused on the caregiver's reaction to problematic behaviors (memory-related problems, depression, and disruptive behaviors) in patients with dementia	24; 0–96; higher scores worse	
Patient and Caregiver Quality of Life			
Quality of Life in Alzheimer's Disease (QOL-AD)[478]	• Patients and caregivers typically complete the QOL-AD separately • 13-items that measure the domains of physical condition, mood, memory, functional abilities, interpersonal relationships, ability to participate in meaningful activities, financial situation, and global assessments of self as a whole and QOL as a whole	13; 13–52; higher scores better	*Higher scores indicate better quality of life for all listed QOL instruments. Unclear interpretation of specific scores.*
Dementia Quality of Life (DEMQOL)[479]	• Patient- or proxy-reported • Addresses 5 domains: daily activities and looking after yourself, health and well-being, cognitive functioning, social relationships and self-concept	28; 28–112; higher scores better	
EuroQOL-5 dimensions (EQ-5D)[480]	• Patient- or proxy-reported health-related quality of life • Has 2 core components: a description of the respondent's own health using a health state classification system with 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a rating on a visual analog thermometer scale	5; 0–100; higher scores better	

Appendix A Table 3. Assessment Scales Commonly Used in Included Trials

Domain/Scale	Description	Number of items; range; direction	Clinical Interpretation
Short Form Health Survey –36 Item (SF-36)/Short Form Health Survey –12 Item (SF-12)[481]	• Patient- or proxy-reported (patient); self-administered (caregiver) • Organized into 8 multi-item scales including physical functioning; role limitations due to physical health (Role functioning/physical); role limitations due to emotional problems (Role functioning/emotional); energy/fatigue (vitality); emotional well-being (mental health); social functioning; pain; general health	SF-36: 36; 0–100; higher scores better SF-12: 12; 0–100; higher scores better	

Appendix B. Literature Flow Diagram



Appendix C. List of Included Studies

Below is a list of included studies and their ancillary publications (indented below main results publication):

KQ1 and KQ3

No studies were identified.

KQ2

1. Ayalon L. The IQCODE Versus a Single-Item Informant Measure to Discriminate Between Cognitively Intact Individuals and Individuals With Dementia or Cognitive Impairment. J Geriatr Psychiatry Neurol. 2011;24(3):168-73. PMID: 21856971. http://dx.doi.org/10.1177/0891988711418506
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8. Cook SE, Marsiske M, McCoy KJ. The use of the Modified Telephone Interview for Cognitive Status (TICS-M) in the detection of amnestic mild cognitive impairment. J Geriatr Psychiatry Neurol. 2009;22(2):103-9. PMID: 19417219. http://dx.doi.org/10.1177/0891988708328214

9. Cruz-Orduna I, Bellon JM, Torrero P, et al. Detecting MCI and dementia in primary care: efficiency of the MMS, the FAQ and the IQCODE. Fam Pract. 2012;29(4):401-6. PMID: 22121012. http://dx.doi.org/10.1093/fampra/cmr114

    a. Olazaran J, Torrero P, Cruz I, et al. Mild cognitive impairment and dementia in primary care: the value of medical history. Fam Pract. 2011;28(4):385-92. PMID: 21402661. http://dx.doi.org/10.1093/fampra/cmr005

10. Cullen B, Fahy S, Cunningham CJ, et al. Screening for dementia in an Irish community sample using MMSE: a comparison of norm-adjusted versus fixed cut-points. Int J Geriatr Psychiatry. 2005;20(4):371-6. PMID: 15799072. http://dx.doi.org/10.1002/gps.1291

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    c. Prick AE, de Lange J, Scherder E, et al. The Effects of a Multicomponent Dyadic Intervention With Physical Exercise on the Cognitive Functioning of People With Dementia: A Randomized Controlled Trial. J Aging Phys Act. 2017:1-14. PMID: 28120631. http://dx.doi.org/10.1123/japa.2016-0038

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Appendix D. List of Excluded Studies

Exclusion Code and Definition
E1. Study relevance **E1b.** Treatment trial with primary prevention; healthy population without dementia or MCI
E2. Study design **E2a.** Not an included study design (be more specific if E2b-E2e apply) **E2b.** Comparative effectiveness **E2c.** Followup <3 months (does not apply for harms) **E2d.** Case-control (for KQ2 only) **E2e.** Cohort or case-control n<1000 (KQ5 only) **E2f.** No comparator/unexposed group (specific to harms outcomes)
E3. Setting **E3a.** Not conducted in 'very high' HDI country **E3b.** Intermediate care facility (nursing home, rehabilitation facility, subacute care) **E3c.** Other unrepresentative setting (hospital, emergency department; KQ2: memory, dementia clinics)
E4. Population **E4a.** Mean age <65 years **E4b.** Exclusively among those with depression or psychosis, alcohol use disorder, HIV/AIDS, Down syndrome, posttraumatic brain injury, metabolic disorders, Parkinson's disease, Huntington's disease, or stroke **E4c.** Severe dementia **E4d.** Professional caregiver **E4e.** Not representative of community-dwelling population (e.g., patients needed to have a sign of cognitive decline during the clinical investigation) (KQ2 only)
E5. Outcomes: No relevant outcomes
E6a. Screener: Not a relevant screening instrument (e.g., time for test administration too long [>10 min clinician, >20 min self], assessment battery [vs. screening instrument]) **E6b.** Intervention: Not one of the specified interventions/treatments **E6c.** Intervention aim: Focused on improving symptoms (mood, neuropsychiatric symptoms) or functional performance or reducing falls
E7b. Does not use a reference standard **E7c.** Study quality (general)
E8. Ancillary study to excluded primary study

1. Abdel-Aziz, K, Larner, AJ. Six-item cognitive impairment test (6CIT): pragmatic diagnostic accuracy study for dementia and MCI. Int Psychogeriatr. 27(6): 991-7. 2015. PMID: 25630996. https://dx.doi.org/10.1017/S1041610214002932 **KQ2E3c**
2. Abdin, E, Vaingankar, JA, et al. Validation of the short version of the 10/66 dementia diagnosis in multiethnic Asian older adults in Singapore. BMC Geriatr. 17(1): 94. 2017. PMID: 28431511. https://dx.doi.org/10.1186/s12877-017-0475-7 **KQ2E1**
3. Adachi, H, Shinagawa, S, et al. Comparison of the utility of everyday memory test and the Alzheimer's Disease Assessment Scale-Cognitive part for evaluation of mild cognitive impairment and very mild Alzheimer's disease. Psychiatry Clin Neurosci. 67(3): 148-53. 2013. PMID: 23581865. https://dx.doi.org/10.1111/pcn.12034 **KQ2E1**
4. Adapt-Fs Research Group. Follow-up evaluation of cognitive function in the randomized Alzheimer's Disease Anti-inflammatory Prevention Trial and its Follow-up Study. Alzheimer's & Dementia. 11(2): 216-25.e1. 2015. PMID: 25022541. https://dx.doi.org/10.1016/j.jalz.2014.03.009 **KQ4E1b, KQ5E1b**
5. Aguiar, P, Monteiro, L, et al. Rivastigmine transdermal patch and physical exercises for Alzheimer's disease: a randomized clinical trial. Curr Alzheimer Res. 11(6): 532-7. 2014. PMID: 24938502. **KQ4E3a, KQ5E3a**
6. Alagiakrishnan, K, Zhao, N, et al. Montreal Cognitive Assessment is superior to Standardized Mini-Mental Status Exam in detecting mild cognitive impairment in the middle-aged and elderly patients with type 2 diabetes mellitus. [Erratum appears in Biomed Res Int. 2014;2014:648472]. Biomed Res Int. 2013(): 186106. 2013. PMID: 23936778. https://dx.doi.org/10.1155/2013/186106 **KQ2E4b**

Appendix D. List of Excluded Studies

7. Alva, G, Cummings, JL, et al. Skin reactions at the application site of rivastigmine patch (4.6 mg/24 h, 9.5 mg/24 h or 13.3 mg/24 h): a qualitative analysis of clinical studies in patients with Alzheimer's disease. Int J Clin Pract. 69(5): 518-30. 2015. PMID: 25684069. https://dx.doi.org/10.1111/ijcp.12621 **KQ4E2a, KQ5E2a**
8. Andersen, F, Viitanen, M, et al. The effect of stimulation therapy and donepezil on cognitive function in Alzheimer's disease. A community based RCT with a two-by-two factorial design. BMC Neurol. 12: 59. 2012. PMID: 22813231. https://dx.doi.org/10.1186/1471-2377-12-59 **KQ4E2a, KQ5E2a**
9. Andrieu, Sandrine, Guyonnet, Sophie, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomised, placebo-controlled trial. The Lancet Neurology. 16(5): 377-389. 2017. https://dx.doi.org/10.1016/S1474-4422%2817%2930040-6 **KQ4E1b, KQ5E1b**
10. Apostolo, JLA, Paiva, DDS, et al. Adaptation and validation into Portuguese language of the six-item cognitive impairment test (6CIT). Aging Ment Health. 1-6. 2017. PMID: 28741373. https://dx.doi.org/10.1080/13607863.2017.1348473 **KQ2E7b**
11. Arabi, Z, Aziz, NA, et al. Early Dementia Questionnaire (EDQ): a new screening instrument for early dementia in primary care practice. BMC Fam Pract. 14: 49. 2013. PMID: 23586732. https://dx.doi.org/10.1186/1471-2296-14-49 **KQ2E3a**
12. Arabi, Z, Syed Abdul Rahman, SA, et al. Reliability and construct validity of the Early Dementia Questionnaire (EDQ). BMC Geriatr. 16(1): 202. 2016. PMID: 27903242. https://dx.doi.org/10.1186/s12877-016-0384-1 **KQ2E3a**
13. Arai, H, Sumitomo, K, et al. Disease state changes and safety of long-term donepezil hydrochloride administration in patients with Alzheimer's disease: interim results from the long-term, large-scale J-GOLD study in Japan. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society. 16(2): 107-15. 2016. PMID: 26114729. https://dx.doi.org/10.1111/psyg.12130 **KQ4E2a, KQ5E2a**
14. Araki, T, Wake, R, et al. The effects of combine treatment of memantine and donepezil on Alzheimer's disease patients and its relationship with cerebral blood flow in the prefrontal area. Int J Geriatr Psychiatry. 29(9): 881-9. 2014. PMID: 24436135. https://dx.doi.org/10.1002/gps.4074 **KQ4E2b, KQ5E2b**
15. Arcoverde, C, Deslandes, A, et al. Treadmill training as an augmentation treatment for Alzheimer's disease: a pilot randomized controlled study. Arq Neuropsiquiatr. 72(3): 190-6. 2014. PMID: 24676435. **KQ4E6b**
16. Arlt, S, Muller-Thomsen, T, et al. Effect of one-year vitamin C- and E-supplementation on cerebrospinal fluid oxidation parameters and clinical course in Alzheimer's disease. Neurochem Res. 37(12): 2706-14. 2012. PMID: 22878647. https://dx.doi.org/10.1007/s11064-012-0860-8 **KQ4E7c, KQ5E7c**
17. Atri, A, Hendrix, SB, et al. Cumulative, additive benefits of memantine-donepezil combination over component monotherapies in moderate to severe Alzheimer's dementia: a pooled area under the curve analysis. Alzheimers Res Ther. 7(1): 28. 2015. PMID: 25991927. https://dx.doi.org/10.1186/s13195-015-0109-2 **KQ4E2a, KQ5E2a**
18. Awata, S, Sugiyama, M, et al. Development of the dementia assessment sheet for community-based integrated care system. Geriatr Gerontol Int. 16 Suppl 1: 123-31. 2016. PMID: 27018290. https://dx.doi.org/10.1111/ggi.12727 **KQ2E6a**
19. Babacan-Yildiz, G, Isik, AT, et al. COST: Cognitive State Test, a brief screening battery for Alzheimer disease in illiterate and literate patients. Int Psychogeriatr. 25(3): 403-12. 2013. PMID: 23137551. https://dx.doi.org/10.1017/S1041610212001780 **KQ2E3a**
20. Babai, S, Auriche, P, et al. Comparison of adverse drug reactions with donepezil versus memantine: analysis of the French Pharmacovigilance Database. Therapie.

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65(3): 255-259. 2010. PMID: 20699079. **KQ5E2f**

21. Bademli K, Lok N, Canbaz M, et al. Effects of Physical Activity Program on cognitive function and sleep quality in elderly with mild cognitive impairment: A randomized controlled trial. Perspect Psychiatr Care. 2018. PMID: 30430592. **KQ4E3b, KQ5E3b**
22. Bahar-Fuchs, A, Webb, S, et al. Tailored and Adaptive Computerized Cognitive Training in Older Adults at Risk for Dementia: A Randomized Controlled Trial. J Alzheimers Dis. 60(3): 889-911. 2017. PMID: 28922158. https://dx.doi.org/10.3233/JAD-170404 **KQ4E2b, KQ5E2b**
23. Baleztena J, Ruiz-Canela M, Sayon-Orea C, et al. Association between cognitive function and supplementation with omega-3 PUFAs and other nutrients in 75 years old patients: a randomized multicenter study. Plos one. 2018. **KQ4E1b, KQ5E1b**
24. Ballard, C, Margallo-Lana, M, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. BMJ. 330(7496): 874. 2005. PMID: 15722369. https://dx.doi.org/10.1136/bmj.38369.459988.8F **KQ4E3b, KQ5E3b**
25. Ballard, C, Thomas, A, et al. A double-blind randomized placebo-controlled withdrawal trial comparing memantine and antipsychotics for the long-term treatment of function and neuropsychiatric symptoms in people with Alzheimer's disease (MAIN-AD). J Am Med Dir Assoc. 16(4): 316-22. 2015. PMID: 25523285. https://dx.doi.org/10.1016/j.jamda.2014.11.002 **KQ4E2b, KQ5E2b**
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28. Barekatain, M, Alavirad, M, et al. Cognitive rehabilitation in patients with nonamnestic mild cognitive impairment. Journal of research in medical sciences. 21(7). 2016. **KQ4E3a, KQ5E3a**
29. Barnes, DE, Beiser, AS, et al. Development and validation of a brief dementia screening indicator for primary care. Alzheimer's & Dementia. 10(6): 656-665.e1. 2014. PMID: 24491321. https://dx.doi.org/10.1016/j.jalz.2013.11.006 **KQ2E1**
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33. Beer, C, Horner, B, et al. A cluster-randomised trial of staff education to improve the quality of life of people with dementia living in residential care: the DIRECT study. PLoS One. 6(11): e28155. 2011. PMID: 22140531. **KQ4E3b, KQ5E3b**
34. Beer, CD, Horner, B, et al. Dementia in residential care: education intervention trial (DIRECT); protocol for a randomised controlled trial. Trials. 11: 63. 2010. PMID: 20500891. **KQ4E8, KQ5E8**
35. Ben-Sadoun, G, Sacco, G, et al. Physical and cognitive stimulation using an Exergame in subjects with normal aging, mild and moderate cognitive impairment. Journal of alzheimers disease. 53(4): 1299-1314. 2016. **KQ4E2a, KQ5E2a**

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38. Bernier, PJ, Gourdeau, C, et al. Validation and diagnostic accuracy of predictive curves for age-associated longitudinal cognitive decline in older adults. CMAJ. 189(48): E1472-E1480. 2017. PMID: 29203616. https://dx.doi.org/10.1503/cmaj.160792 **KQ2E1**
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50. Brijoux T, Kricheldorff C, M HL, et al. Supporting Families Living With Dementia in Rural Areas. Dtsch. 2016;113(41):681-7. PMID: 27839534. **KQ4E2b, KQ5E2b**

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51. Brijoux, Thomas, Kricheldorff, Cornelia, et al. Supporting families living with dementia in rural areas: A randomized controlled trial of quality of life improvement using qualified volunteers. Dtsch Arztebl Int. 113(41): 681-689. 2016. **KQ4E2b, KQ5E2b**
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55. Brodaty, H, Gresham, M. Effect of a training programme to reduce stress in carers of patients with dementia. BMJ. 299(6712): 1375-1379. 1989. PMID: 2513967. **KQ4E3c, KQ5E3c**
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63. Cabrera, AG, Pena, MC, et al. Early detection of cognitive disorders: Follow-up study. Can J Neurosci Nurs. 37(2): 42-6. 2015. PMID: 26647494. **KQ2E7b**
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65. Callahan, CM, Boustani, MA, et al. Alzheimer's disease multiple intervention trial (ADMIT): study protocol for a randomized controlled clinical trial. Trials [Electronic Resource]. 13: 92. 2012. PMID: 22737979. https://dx.doi.org/10.1186/1745-6215-13-92 **KQ4E2b, KQ5E2b**
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https://dx.doi.org/10.7326/M16-0830 **KQ4E2b, KQ5E2b**

67. Campbell, NL, Perkins, AJ, et al. Adherence and Tolerability of Alzheimer's Disease Medications: A Pragmatic Randomized Trial. J Am Geriatr Soc. 65(7): 1497-1504. 2017. PMID: 28295141. https://dx.doi.org/10.1111/jgs.14827 **KQ4E2b, KQ5E2b**
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69. Caramelli, P, Laks, J, et al. Effects of galantamine and galantamine combined with nimodipine on cognitive speed and quality of life in mixed dementia: a 24-week, randomized, placebo-controlled exploratory trial (the REMIX study). Arq Neuropsiquiatr. 72(6): 411-7. 2014. PMID: 24964105. **KQ4E3a, KQ5E3a**
70. Carnero-Pardo, C, Cruz-Orduna, I, et al. Utility of the mini-cog for detection of cognitive impairment in primary care: Data from two spanish studies. Int J Alzheimers Dis. 2013. https://dx.doi.org/10.1155/2013/285462 **KQ2E4e**
71. Carretti, B, Borella, E, et al. Benefits of training working memory in amnestic mild cognitive impairment: specific and transfer effects. Int Psychogeriatr. 25(4): 617-26. 2013. PMID: 23253363. https://dx.doi.org/10.1017/S1041610212002177 **KQ4E2b, KQ5E2b**
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73. Castanho, TC, Portugal-Nunes, C, et al. Applicability of the Telephone Interview for Cognitive Status (Modified) in a community sample with low education level: association with an extensive neuropsychological battery. Int J Geriatr Psychiatry. 31(2): 128-36. 2016. PMID: 25963399. https://dx.doi.org/10.1002/gps.4301 **KQ2E7c**
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75. Chan, AW, Yu, DS, et al. Tai chi qigong as a means to improve night-time sleep quality among older adults with cognitive impairment: a pilot randomized controlled trial. Clin Interv Aging. 11(): 1277-1286. 2016. PMID: 27698557. https://dx.doi.org/10.2147/CIA.S111927 **KQ4E6c, KQ5E6c**
76. Chan, J, Churcher Clarke, A, et al. A Mindfulness Program Manual for People With Dementia. Behav Modif. 41(6): 764-787. 2017. PMID: 28689469. https://dx.doi.org/10.1177/0145445517715872 **KQ4E2a, KQ5E2a**
77. Chang W, Teng J. Combined application of tenuigenin and beta-asarone improved the efficacy of memantine in treating moderate-to-severe Alzheimer's disease. Drug Des Devel Ther. 2018;12:455-62. PMID: 29551889. **KQ4E3a, KQ5E3a**
78. Charernboon, T. Diagnostic Accuracy of the Overlapping Infinity Loops, Wire Cube, and Clock Drawing Tests for Cognitive Impairment in Mild Cognitive Impairment and Dementia. Int J Alzheimers Dis. 2017(): 5289239. 2017. PMID: 28255496. https://dx.doi.org/10.1155/2017/5289239 **KQ2E3a**
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International Psychogeriatrics. 2018;30(8):1189-97. PMID: 29223190. **KQ2E2a**

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84. Chen, HM, Huang, MF, et al. Effectiveness of coping strategies intervention on caregiver burden among caregivers of elderly patients with dementia. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society. 15(1): 20-5. 2015. PMID: 25515800. https://dx.doi.org/10.1111/psyg.12071 **KQ4E7c, KQ5E7c**
85. Cheng, ST, Fung, HH, et al. Short-Term Effects of a Gain-Focused Reappraisal Intervention for Dementia Caregivers: A Double-Blind Cluster-Randomized Controlled Trial. American Journal of Geriatric Psychiatry. 24(9): 740-50. 2016. PMID: 27401052. https://dx.doi.org/10.1016/j.jagp.2016.04.012 **KQ4E2b, KQ5E2b**
86. Chenoweth, L, Jeon, YH, et al. PerCEN trial participant perspectives on the implementation and outcomes of person-centered dementia care and environments. Int Psychogeriatr. 27(12): 2045-57. 2015. PMID: 26307245. https://dx.doi.org/10.1017/S1041610215001350 **KQ4E3b, KQ5E3b**
87. Chenoweth L, Stein-Parbury J, White D, et al. Coaching in self-efficacy improves care responses, health and well-being in dementia carers: a pre/post-test/follow-up study. BMC health services research. 2016;16(pp 166). PMID: 27146060. **KQ4E2a, KQ5E2a**
88. Cherrier, MM, Anderson, K, et al. Testosterone treatment of men with mild cognitive impairment and low testosterone levels. Am J Alzheimers Dis Other Demen. 30(4): 421-30. 2015. PMID: 25392187. https://dx.doi.org/10.1177/1533317514556874 **KQ4E4b, KQ5E4b**
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90. Cheung, Karen Siu-Lan, Lau, Bobo Hi-Po, et al. Multicomponent intervention on enhancing dementia caregiver well-being and reducing behavioral problems among Hong Kong Chinese: A translational study based on REACH II. Int J Geriatr Psychiatry. 30(5): 460-469. 2015. https://dx.doi.org/10.1002/gps.4160 **KQ4E2a, KQ5E2a**
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https://dx.doi.org/10.1111/ggi.12464 **KQ2E2d**

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99. Clarfield, AM, Dwolatzky, T. Exercise in Alzheimer disease: comment on "Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial". JAMA Intern Med. 173(10): 901-2. 2013. PMID: 23588877. https://dx.doi.org/10.1001/jamainternmed.2013.1215 **KQ4E5, KQ5E5**
100. Clarke, R, Harrison, G, et al. Effect of vitamins and aspirin on markers of platelet activation, oxidative stress and homocysteine in people at high risk of dementia. J Intern Med. 254(1): 67-75. 2003. PMID: 12823643. **KQ4E2b, KQ5E2b**
101. Clarnette, R, O'Caoimh, R, et al. Comparison of the Quick Mild Cognitive Impairment (Qmci) screen to the Montreal Cognitive Assessment (MoCA) in an Australian geriatrics clinic. Int J Geriatr Psychiatry. 32(6): 643-649. 2017. PMID: 27427212. https://dx.doi.org/10.1002/gps.4505 **KQ2E2d**
102. Coelho, FG, Andrade, LP, et al. Multimodal exercise intervention improves frontal cognitive functions and gait in Alzheimer's disease: a controlled trial. Geriatr Gerontol Int. 13(1): 198-203. 2013. PMID: 22686565. https://dx.doi.org/10.1111/j.1447-0594.2012.00887.x **KQ4E3a, KQ5E3a**
103. Collaborative Group AD, Bentham, P, Gray, et al. Aspirin in Alzheimer's disease (AD2000): a randomised open-label trial. Lancet Neurol. 7(1): 41-9. 2008. PMID: 18068522. https://dx.doi.org/10.1016/S1474-4422(07)70293-4 **KQ4E2a, KQ5E2a**
104. Coley N, Raman R, Donohue MC, et al. Defining the Optimal Target Population for Trials of Polyunsaturated Fatty Acid Supplementation Using the Erythrocyte Omega-3 Index: A Step Towards Personalized Prevention of Cognitive Decline? Journal of Nutrition, Health & Aging. 2018;22(8):982-98. PMID: 30272103. **KQ4E1b, KQ5E1b**
105. Connon, P, Larner, AJ. Six-item Cognitive Impairment Test (6CIT): diagnostic test accuracy study in primary care referrals. Int J Geriatr Psychiatry. 32(5): 583-584. 2017. PMID: 28379632. https://dx.doi.org/10.1002/gps.4692 **KQ2E3c**
106. Cooper, C, Barber, J, et al. Effectiveness of START psychological intervention in reducing abuse by dementia family carers: randomized controlled trial. Int Psychogeriatr. 28(6): 881-7. 2016. PMID: 26652193. https://dx.doi.org/10.1017/S1041610215002033 **KQ4E5, KQ5E5**
107. Cornelis, E, Gorus, E, et al. Early diagnosis of mild cognitive impairment and mild dementia through basic and instrumental activities of daily living: Development of a new evaluation tool. PLoS Medicine / Public Library of Science. 14(3): e1002250. 2017. PMID: 28291801. https://dx.doi.org/10.1371/journal.pmed.1002250 **KQ2E2d**
108. Cothran, FA, Paun, O, et al. Comparing the Effect of a Moderate Physical Activity Intervention on the Mental Health Outcomes of African American and Caucasian Dementia Family Caregivers: A Secondary Data Analysis. Issues Ment Health Nurs. 1-9. 2017. PMID: 28956706. https://dx.doi.org/10.1080/01612840.2017.1364807 **KQ4E2b, KQ5E2b**
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https://dx.doi.org/10.2147/CIA.S38420 **KQ4E7c**, **KQ5E7c**

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111. Creavin, S, Fish, M, et al. Clinical history for diagnosis of dementia in men: Caerphilly Prospective Study. Br J Gen Pract. 65(637): e489-99. 2015. PMID: 26212844. https://dx.doi.org/10.3399/bjgp15X686053 **KQ2E1**
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burden in dementia: Preliminary results from a randomized trial of the tailored activity program-outpatient version. Int J Geriatr Psychiatry. 2018. PMID: 30035341. **KQ4E3a, KQ5E3a**

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125. DeGregory, Cristy. The effects of multiple gratitude interventions among informal caregivers of persons with dementia and Alzheimer's disease. 148 p. 2014. **KQ4E2c, KQ5E2c**
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156. Freitas, S, Prieto, G, et al. Psychometric properties of the Montreal Cognitive Assessment (MoCA): an analysis using the Rasch model. Clinical Neuropsychologist. 28(1): 65-83. 2014. PMID: 24404822. https://dx.doi.org/10.1080/13854046.2013.870231 **KQ2E1**
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158. Fung AW, Lam LCW. Validation of a computerized Hong Kong - vigilance and memory test (HK-VMT) to detect early cognitive impairment in healthy older adults. Aging Ment Health. 2018:1-7. PMID: 30270640. **KQ2E2d**
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161. Gallagher-Thompson, D, Tzuang, M, et al. Effectiveness of a fotonovela for reducing depression and stress in Latino dementia family caregivers. Alzheimer Dis Assoc Disord. 29(2): 146-53. 2015. PMID: 25590939. https://dx.doi.org/10.1097/WAD.0000000000000077 **KQ4E7c, KQ5E7c**
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175. Gonyea, JG, Lopez, LM, et al. The Effectiveness of a Culturally Sensitive Cognitive Behavioral Group Intervention for Latino Alzheimer's Caregivers. Gerontologist. 56(2): 292-302. 2016. PMID: 24855313. https://dx.doi.org/10.1093/geront/gnu045 **KQ4E2b, KQ5E2b**
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184. Grober, E, Mowrey, WB, et al. Two-stage screening for early dementia in primary care. Journal of Clinical & Experimental Neuropsychology: Official Journal of the International Neuropsychological Society. 38(9): 1038-49. 2016. PMID: 27270103. https://dx.doi.org/10.1080/13803395.2016.1187117 **KQ2E7c**
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194. Hagovska, M, Dzvonik, O, et al. Comparison of Two Cognitive Training Programs With Effects on Functional Activities and Quality of Life. Res Gerontol Nurs. 10(4): 172-180. 2017. https://dx.doi.org/10.3928/19404921-20170524-01 **KQ4E2b, KQ5E2b**
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196. Hagovska, M, Takac, P, et al. Effect of a combining cognitive and balanced training on the cognitive, postural and functional status of seniors with a mild cognitive deficit in a randomized, controlled trial. European journal of physical & rehabilitation medicine. 52(1): 101-9. 2016. PMID: 26325026. **KQ4E2c, KQ5E2c**
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202. Han JW, Son KL, Byun HJ, et al. Efficacy of the Ubiquitous Spaced Retrieval-based Memory Advancement and Rehabilitation Training (USMART) program among patients with mild cognitive impairment: a randomized controlled crossover trial. Alzheimers Res Ther. 2017;9(1):39. PMID: 28587629. **KQ4E2c, KQ5E2c**
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204. Harris, JonathanB, Johnson, C. The impact of physical versus social activity on the physical and cognitive functioning of seniors with dementia. Act Adapt Aging. 41(2): 161-174. 2017. https://dx.doi.org/10.1080/01924788.2017.1306383 **KQ4E3b, KQ5E3b**
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208. Hessler, J, Bronner, M, et al. Suitability of the 6CIT as a screening test for dementia in primary care patients. Aging Ment Health. 18(4): 515-20. 2014. PMID: 24256425. https://dx.doi.org/10.1080/13607863.2013.856864 **KQ2E7b**
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210. Hilsabeck, RC, Holdnack, JA, et al. The Brief Cognitive Status Examination (BCSE): Comparing Diagnostic Utility and Equating Scores to the Mini-Mental State Examination (MMSE). Archives of Clinical Neuropsychology. 30(5): 458-67. 2015. PMID: 26085478. https://dx.doi.org/10.1093/arclin/acv037 **KQ2E4e**
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Br J Sports Med. 2017. PMID: 28432077. https://dx.doi.org/10.1136/bjsports-2016-096846 **KQ4E5, KQ5E5**

213. Huang, HL, Shyu, YI, et al. A pilot study on a home-based caregiver training program for improving caregiver self-efficacy and decreasing the behavioral problems of elders with dementia in Taiwan. Int J Geriatr Psychiatry. 18(4): 337-345. 2003. PMID: 12673611. **KQ4E5, KQ5E5**
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215. Ilhan Algin, D, Dagli Atalay, S, et al. Memantine improves semantic memory in patients with amnestic mild cognitive impairment: A single-photon emission computed tomography study. J Int Med Res. 300060517715166. 2017. PMID: 28661262. https://dx.doi.org/10.1177/0300060517715166 **KQ4E3a, KQ5E3a**
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impairment?. Int Psychogeriatr. 25(4): 627-34. 2013. PMID: 23253431. https://dx.doi.org/10.1017/S1041610212002207 **KQ2E2d**

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229. Kan CN, Zhang L, Cheng CY, et al. The Informant AD8 Can Discriminate Patients with Dementia From Healthy Control Participants in an Asian Older Cohort. J Am Med Dir Assoc. 2019. PMID: 30661859. **KQ2E4e**
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231. Kamkhagi, D, Costa, Aco, et al. Benefits of psychodynamic group therapy on depression, burden and quality of life of family caregivers to Alzheimer's disease patients. Revista de psiquiatria clinica. 42(6): 157-160. 2015. https://dx.doi.org/10.1590/0101-60830000000067 **KQ4E3a, KQ5E3a**
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240. Kim, JW, Lee, DY, et al. Improvement of dementia screening accuracy of mini-mental state examination by education-adjustment and supplementation of frontal assessment battery performance. J Korean Med Sci. 28(10): 1522-8. 2013. PMID: 24133360. https://dx.doi.org/10.3346/jkms.2013.28.10.1522 **KQ2E3c**
241. Kim, JW, Lee, DY, et al. Improvement of Screening Accuracy of Mini-Mental State Examination for Mild Cognitive Impairment and Non-Alzheimer's Disease Dementia by Supplementation of Verbal

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Fluency Performance. Psychiatry Investig. 11(1): 44-51. 2014. PMID: 24605123. https://dx.doi.org/10.4306/pi.2014.11.1.44 **KQ2E3c**

242. Kim, M-J, Han, C-W, et al. Physical Exercise with Multicomponent Cognitive Intervention for Older Adults with Alzheimer's Disease: a 6-Month Randomized Controlled Trial. Dement Geriatr Cogn Dis Extra. 6(2): 222-232. 2016. https://dx.doi.org/10.1159/000446508 **KQ4E3b, KQ5E3b**
243. Kiosses, DN, Ravdin, LD, et al. Problem Adaptation Therapy for Older Adults With Major Depression and Cognitive Impairment: A Randomized Clinical Trial. JAMA Psychiatry. 72(1): 22-30. 2015. PMID: 25372657. **KQ4E4b, KQ5E4b**
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245. Kohanpour, M-A, Peeri, M, et al. The effects of aerobic exercise with lavender essence use on cognitive state and serum brain-derived neurotrophic factor levels in elderly with mild cognitive impairment. Journal of herbmed pharmacology. 6(2): 80-84. 2017. **KQ4E3a, KQ5E3a**
246. Kohanpour M-A, Peeri M, Azarbayjani M-A. The Effects of Glycyrrhiza glabra L. extract use with aerobic training on inflammatory factors and cognitive state in elderly with mild cognitive impairment. Journal of herbmed pharmacology. 2017;6(4):178-84. **KQ4E3a, KQ5E3a**
247. Kohler, L, Meinke-Franze, C, et al. Does an interdisciplinary network improve dementia care? Results from the IDemUck-study. Curr Alzheimer Res. 11(6): 538-48. 2014. PMID: 24938504. **KQ4E7c, KQ5E7c**
248. Koontz, J, Baskys, A. Effects of galantamine on working memory and global functioning in patients with mild cognitive impairment: a double-blind placebo-controlled study. Am J Alzheimers Dis Other Demen. 20(5): 295-302. 2005. PMID: 16273995. **KQ4E7c, KQ5E7c**
249. Kroger, E, Mouls, M, et al. Adverse Drug Reactions Reported With Cholinesterase Inhibitors: An Analysis of 16 Years of Individual Case Safety Reports From VigiBase. Annals of Pharmacotherapy. 49(11): 1197-206. 2015. PMID: 26324356. https://dx.doi.org/10.1177/1060028015602274 **KQ5E2a**
250. Kroger, E, Van Marum, R, et al. Treatment with rivastigmine or galantamine and risk of urinary incontinence: results from a Dutch database study. Pharmacoepidemiol Drug Saf. 24(3): 276-85. 2015. PMID: 25652526. https://dx.doi.org/10.1002/pds.3741 **KQ5E2a**
251. Kuo LM, Huang HL, Huang HL, et al. A home-based training program improves Taiwanese family caregivers' quality of life and decreases their risk for depression: a randomized controlled trial. Int J Geriatr Psychiatry. 2013;28(5):504-13. PMID: 22778053. **KQ4E4c, KQ5E4c**
252. Kuo, LM, Huang, HL, et al. Health-related quality of life and self-efficacy of managing behavior problems for family caregivers of vascular dementia and Alzheimer's disease patients. Dement Geriatr Cogn Disord. 38(5-6): 310-20. 2014. PMID: 25011490. https://dx.doi.org/10.1159/000360414 **KQ4E5, KQ5E5**
253. Kurz, A, Grimmer, T. Efficacy of memantine hydrochloride once-daily in Alzheimer's disease. Expert Opin Pharmacother. 15(13): 1955-60. 2014. PMID: 25085661. https://dx.doi.org/10.1517/14656566.2014.945907 **KQ4E5, KQ5E5**
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258. Lacey, L, Bobula, J, et al. Informal Care Time and Cost in a Large Clinical Trial Sample of Patients with Mild to Moderate Alzheimer's Disease: determinants and Level of Change Observed. Neurology and therapy. 6(1): 11-23. 2017. https://dx.doi.org/10.1007/s40120-016-0056-2 **KQ4E5, KQ5E5**
259. Laforce, R, Jr, Sellami, et al. Validation of the Depistage Cognitif de Quebec: A New Cognitive Screening Tool for Atypical Dementias. Arch Clin Neuropsychol. 1-9. 2017. PMID: 28541543. https://dx.doi.org/10.1093/arclin/acx048 **KQ2E1**
260. Lai, EC, Wong, MB, et al. Risk of pneumonia in new users of cholinesterase inhibitors for dementia. J Am Geriatr Soc. 63(5): 869-76. 2015. PMID: 25912671. https://dx.doi.org/10.1111/jgs.13380 **KQ4E2a, KQ5E2a**
261. Lam, LC, Chan, WM, et al. Effectiveness of Tai Chi in maintenance of cognitive and functional abilities in mild cognitive impairment: a randomised controlled trial. Hong Kong Medical Journal. 20(3 Suppl 3): 20-3. 2014. PMID: 25001031. **KQ4E7c, KQ5E7c**
262. LaMantia, MA, Alder, CA, et al. The Aging Brain Care Medical Home: Preliminary Data. J Am Geriatr Soc. 63(6): 1209-13. 2015. PMID: 26096394. https://dx.doi.org/10.1111/jgs.13447 **KQ4E2a, KQ5E2a**
263. Langoni CDS, Resende TL, Barcellos AB, et al. Effect of Exercise on Cognition, Conditioning, Muscle Endurance, and Balance in Older Adults With Mild Cognitive Impairment: A Randomized Controlled Trial. Journal of geriatric physical therapy (2001). 2018. PMID: 29738405. **KQ4E3a, KQ5E3a**
264. Langoni CDS, Resende TL, Barcellos AB, et al. The effect of group exercises on balance, mobility, and depressive symptoms in older adults with mild cognitive impairment: a randomized controlled trial. Clin Rehabil. 2018:269215518815218. PMID: 30514115. **KQ4E1, KQ5E1**
265. Laporte, Uribe F, Graske, J, et al. Regional dementia care networks in Germany: changes in caregiver burden at one-year follow-up and associated factors. Int Psychogeriatr. 1-14. 2017. https://dx.doi.org/10.1017/S1041610217000126 **KQ4E2a, KQ5E2a**
266. Larner, A. MACE versus MoCA: Equivalence or superiority? Pragmatic diagnostic test accuracy study. Int Psychogeriatr. 29(6): 931-937. 2017. https://dx.doi.org/10.1017/S1041610216002210 **KQ2E3c**
267. Larner, AJ. Does combining an informant questionnaire with patient performance scales improve diagnostic test accuracy for cognitive impairment?. Int J Geriatr Psychiatry. 32(4): 466-467. 2017. PMID: 28272789. https://dx.doi.org/10.1002/gps.4647 **KQ2E3c**
268. Larner, AJ. Hard-TYM: a pragmatic study. Int J Geriatr Psychiatry. 30(3): 330-1. 2015. PMID: 25631916. https://dx.doi.org/10.1002/gps.4249 **KQ2E3c**
269. Larner, AJ. Implications of changing the Six-item Cognitive Impairment Test cutoff. Int J Geriatr Psychiatry. 30(7): 778-9. 2015. PMID: 26058457. https://dx.doi.org/10.1002/gps.4303 **KQ2E3c**
270. Larner, AJ. Mini-Addenbrooke's cognitive examination diagnostic accuracy for dementia: reproducibility study. Int J Geriatr Psychiatry. 30(10): 1103-4. 2015. PMID: 26376107. https://dx.doi.org/10.1002/gps.4334 **KQ2E3c**
271. Larner, AJ. Mini-Addenbrooke's Cognitive Examination: a pragmatic diagnostic accuracy study. Int J Geriatr Psychiatry. 30(5): 547-8. 2015. PMID: 25855207. https://dx.doi.org/10.1002/gps.4258 **KQ2E3c**
272. Larner AJ. Mini-Mental State Examination: diagnostic test accuracy study in primary care referrals.

Neurodegenerative Disease Management. 2018;8(5):301-5. PMID: 30223710. **KQ2E4e**

273. Lavery, LL, Lu, SY, et al. Cognitive assessment of older primary care patients with and without memory complaints. J Gen Intern Med. 22(7): 949-954. 2007. PMID: 17453265. https://dx.doi.org/17453265 **KQ2E7c**
274. Lebedeva, E, Gallant, S, et al. Improving the Measurement of Cognitive Ability in Geriatric Patients. Dement Geriatr Cogn Disord. 40(3-4): 148-57. 2015. PMID: 26107499. https://dx.doi.org/10.1159/000381536 **KQ2E5**
275. Lee TM, Chan FH, Chu LW, et al. Auditory-based cognitive training programme for attention and memory in older people at risk of progressive cognitive decline: a randomised controlled trial. Hong Kong Med. 2017;23 Suppl 2(3):12-5. PMID: 29938664. **KQ4E1b, KQ5E1b**
276. Lee SJ, Han JH, Hwang JW, et al. Screening for Normal Cognition, Mild Cognitive Impairment, and Dementia with the Korean Dementia Screening Questionnaire. Psychiatry Investigation. 2018;15(4):384-9. PMID: 29475235. **KQ2E2d**
277. Lee, GY, Yip, CC, et al. Evaluation of a computer-assisted errorless learning-based memory training program for patients with early Alzheimer's disease in Hong Kong: a pilot study. Clin Interv Aging. 8(): 623-33. 2013. PMID: 23766638. https://dx.doi.org/10.2147/CIA.S45726 **KQ4E7c, KQ5E7c**
278. Lee, LK, Shahar, S, et al. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. Psychopharmacology (Berl). 225(3): 605-12. 2013. PMID: 22932777. https://dx.doi.org/10.1007/s00213-012-2848-0 **KQ4E3a, KQ5E3a**
279. Lees, R, Selvarajah, J, et al. Test accuracy of cognitive screening tests for diagnosis of dementia and multidomain cognitive impairment in stroke. Stroke. 45(10): 3008-18. 2014. PMID: 25190446. https://dx.doi.org/10.1161/STROKEAHA.114.005842 **KQ2E2a**
280. Lemke NC, Werner C, Wiloth S, et al. Transferability and Sustainability of Motor-Cognitive Dual-Task Training in Patients with Dementia: A Randomized Controlled Trial. Gerontology. 2019;65(1):68-83. PMID: 30041173. **KQ4E3b, KQ5E3b**
281. Li, F, Harmer, P, et al. Tai Ji Quan and global cognitive function in older adults with cognitive impairment: a pilot study. Arch Gerontol Geriatr. 58(3): 434-9. 2014. PMID: 24398166. https://dx.doi.org/10.1016/j.archger.2013.12.003 **KQ4E2a, KQ5E2a**
282. Li, M, Ng, TP, et al. Brief informant screening test for mild cognitive impairment and early Alzheimer's disease. Dement Geriatr Cogn Disord. 21(5-6): 392-402. 2006. PMID: 16645272. https://dx.doi.org/16645272 **KQ2E3c**
283. Li, R, Cooper, C, et al. Coping strategies as mediators of the effect of the START (strategies for RelaTives) intervention on psychological morbidity for family carers of people with dementia in a randomised controlled trial. J Affect Disord. 168(): 298-305. 2014. PMID: 25083601. https://dx.doi.org/10.1016/j.jad.2014.07.008 **KQ4E5, KQ5E5**
284. Li, T, Yao, Y, et al. Cognitive training can reduce the rate of cognitive aging: a neuroimaging cohort study. BMC Geriatr. 16(): 12. 2016. PMID: 26762334. https://dx.doi.org/10.1186/s12877-016-0194-5 **KQ4E3a, KQ5E3a**
285. Li, X, Jia, S, et al. The Gesture Imitation in Alzheimer's Disease Dementia and Amnestic Mild Cognitive Impairment. J Alzheimers Dis. 53(4): 1577-84. 2016. PMID: 27540963. https://dx.doi.org/10.3233/JAD-160218 **KQ2E3a**
286. Lin, HC, Yang, YP, et al. Distinctive effects between cognitive stimulation and reminiscence therapy on cognitive function and quality of life for different types of behavioural problems in dementia. Scand J Caring Sci. 2017. PMID: 28881430. https://dx.doi.org/10.1111/scs.12484 **KQ4E7c, KQ5E7c**
287. Liu, Xy, Li, L, et al. Cognitive training in older adults with mild cognitive impairment. Biomed Environ Sci. 29(5): 356-364. 2016. **KQ4E3a, KQ5E3a**

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290. Lok, N, Bademli, K. Pilot testing of the "First You Should Get Stronger" program among caregivers of older adults with dementia. Arch Gerontol Geriatr. 68(): 84-89. 2017. PMID: 27689315. https://dx.doi.org/10.1016/j.archger.2016.09.006 **KQ4E2c, KQ5E2c**
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337. Nakamae, T, Yotsumoto, K, et al. Effects of productive activities with reminiscence in occupational therapy for people with dementia: A pilot randomized controlled study. Hong Kong Journal of Occupational Therapy. 24(1): 13-9. 2014. https://dx.doi.org/10.1016/j.hkjot.2014.01.003 **KQ4E6b**, **KQ5E6b**
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341. Ng, A, Chew, I, et al. Effectiveness of Montreal Cognitive Assessment for the diagnosis of mild cognitive impairment and mild Alzheimer's disease in Singapore. Singapore Med J. 54(11): 616-9. 2013. PMID: 24276096. **KQ2E2d**
342. Ng, TP, Feng, L, et al. Montreal Cognitive Assessment for screening mild cognitive impairment: variations in test performance and scores by education in Singapore. Dement Geriatr Cogn Disord. 39(3-4): 176-85. 2015. https://dx.doi.org/10.1159/000368827 **KQ2E2d**
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348. O'Caoimh, R, Gao, Y, et al. Which part of the Quick mild cognitive impairment screen (Qmci) discriminates between normal cognition, mild cognitive impairment and dementia?. Age Ageing. 42(3): 324-30. 2013. PMID: 23612864. https://dx.doi.org/10.1093/ageing/aft044 **KQ2E3c**
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350. Ohnishi, T, Sakiyama, Y, et al. The prediction of response to galantamine treatment in patients with mild to moderate Alzheimer's disease. Curr Alzheimer Res. 11(2): 110-8. 2014. PMID: 24156269. **KQ4E5, KQ5E5**
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353. Okuizumi K, Kamata T, Matsui D, et al. Memantine in Japanese patients with moderate to severe Alzheimer's disease: meta-analysis of multiple-index responder analyses. Expert Opinion on Pharmacotherapy. 2018;19(5):425-30. PMID: 29448852. **KQ4E2a, KQ5E2a**
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older adults with mild cognitive impairment. Ann Neurol. 73(6): 762-73. 2013. PMID: 23447373. https://dx.doi.org/10.1002/ana.23874 **KQ4E5, KQ5E5**

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365. Pariente, A, Sanctussy, DJ, et al. Factors associated with serious adverse reactions to cholinesterase inhibitors: a study of spontaneous reporting. CNS Drugs. 24(1): 55-63. 2010. PMID: 20030419. **KQ5E2f**
366. Park JH, Jung M, Kim J, et al. Validity of a novel computerized screening test system for mild cognitive impairment. International Psychogeriatrics. 2018;30(10):1455-63. PMID: 29923471. **KQ2E2d**
367. Park, KW, Kim, EJ, et al. Efficacy and tolerability of rivastigmine patch therapy in patients with mild-to-moderate Alzheimer's dementia associated with minimal and moderate ischemic white matter hyperintensities: A multicenter prospective open-label clinical trial. PLoS ONE [Electronic Resource]. 12(8): e0182123. 2017. PMID: 28786987. https://dx.doi.org/10.1371/journal.pone.0182123 **KQ4E2a, KQ5E2a**
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378. Pirrotta, Fabio, Timpano, Francesca, et al. Italian validation of Montreal Cognitive Assessment. European Journal of Psychological Assessment. 31(2): 131-137. 2015. https://dx.doi.org/10.1027/1015-5759/a000217 **KQ2E7b**
379. Poptsi E, Lazarou I, Markou N, et al. A Comparative Single-Blind Randomized Controlled Trial With Language Training in People With Mild Cognitive Impairment. American Journal of Alzheimer's Disease & Other Dementias. 2018:1533317518813554. PMID: 30518237. **KQ4E7c, KQ5E7c**
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381. Potkin, SG, Anand, R, et al. Brain metabolic and clinical effects of rivastigmine in Alzheimer's disease. Int J Neuropsychopharmacol. 4(3): 223-30. 2001. PMID: 11602028. https://dx.doi.org/doi:10.1017/S1461145701002528 **KQ4E1, KQ5E1**
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387. Radford, K, Mack, HA, et al. Prevalence of dementia in urban and regional Aboriginal Australians. Alzheimers Dement. 11(3): 271-9. 2015. PMID: 24985534. https://dx.doi.org/10.1016/j.jalz.2014.03.007 **KQ2E8**
388. Rami, L, Mollica, MA, et al. The Subjective Cognitive Decline Questionnaire (SCD-Q): a validation study. J Alzheimers Dis. 41(2): 453-66. 2014. PMID: 24625794. https://dx.doi.org/10.3233/JAD-132027 **KQ2E2d**
389. Ramlall, S, Chipps, J, et al. The sensitivity and specificity of subjective memory complaints and the subjective memory rating scale, deterioration cognitive observee, mini-mental state examination, six-item screener and clock drawing test in dementia screening. Dement Geriatr Cogn Disord. 36(1-2): 119-35. 2013. PMID: 23860433. https://dx.doi.org/10.1159/000350768 **KQ2E3a**
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Appendix D. List of Excluded Studies

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392. Regan, B, Wells, Y, et al. MAXCOG-Maximizing Cognition: A Randomized Controlled Trial of the Efficacy of Goal-Oriented Cognitive Rehabilitation for People with Mild Cognitive Impairment and Early Alzheimer Disease. American Journal of Geriatric Psychiatry. 16(): 16. 2016. PMID: 28034509. https://dx.doi.org/10.1016/j.jagp.2016.11.008 **KQ4E7c**, **KQ5E7c**
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395. Reisberg, Barry, Shao, Yongzhao, et al. Comprehensive, individualized, person-centered management of community-residing persons with moderate-to-severe Alzheimer disease: A randomized controlled trial. Dement Geriatr Cogn Disord. 43(1-2): 100-117. 2017. https://dx.doi.org/10.1159/000455397 **KQ4E4c, KQ5E4c**
396. Relkin, NR, Reichman, WE, et al. A large, community-based, open-label trial of donepezil in the treatment of Alzheimer's disease. Dement Geriatr Cogn Disord. 16(1): 15-24. 2003. PMID: 12714795. **KQ5E2f**
397. Remington, R, Bechtel, C, et al. A Phase II Randomized Clinical Trial of a Nutritional Formulation for Cognition and Mood in Alzheimer's Disease. J Alzheimers Dis. 45(2): 395-405. 2015. PMID: 25589719. https://dx.doi.org/10.3233/JAD-142499 **KQ4E7c**, **KQ5E7c**
398. Requena, C, Lopez Ibor, MI, et al. Effects of cholinergic drugs and cognitive training on dementia. Dement Geriatr Cogn Disord. 18(1): 50-54. 2004. PMID: 15084794. **KQ4E7c, KQ5E7c**
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400. Richarz, U, Gaudig, M, et al. Galantamine treatment in outpatients with mild Alzheimer's disease. Acta Neurol Scand. 129(6): 382-92. 2014. PMID: 24461047. https://dx.doi.org/10.1111/ane.12195 **KQ5E2f**
401. Riepe, MW. High-dose cholinergic therapy with rivastigmine patch does not prolong QTc time in patients with Alzheimer's disease. J Clin Psychiatry. 75(3): 288. 2014. PMID: 24717382. https://dx.doi.org/10.4088/JCP.13l08730 **KQ4E2b, KQ5E2b**
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404. Roalf, DR, Moore, TM, et al. Defining and validating a short form Montreal Cognitive Assessment (s-MoCA) for use in neurodegenerative disease. J Neurol Neurosurg Psychiatry. 87(12): 1303-1310. 2016. PMID: 27071646. https://dx.doi.org/10.1136/jnnp-2015-312723 **KQ2E3c**
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Psychiatry. 25(2): 191-201. 2010. PMID: 19548273. **KQ4E2f, KQ5E2f**

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411. Rokstad AMM, Engedal K, Kirkevold O, et al. The impact of attending day care designed for home-dwelling people with dementia on nursing home admission: a 24-month controlled study. BMC Health Services Research. 2018;18(1):864. PMID: 30445937. **KQ4E6b, KQ5E6b**
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413. Rosa IM, Henriques AG, Wiltfang J, et al. Putative Dementia Cases Fluctuate as a Function of Mini-Mental State Examination Cut-Off Points. Journal of Alzheimer's Disease. 2018;61(1):157-67. PMID: 29125486. **KQ2E7c**
414. Rosa IM, Henriques AG, Carvalho L, et al. Screening Younger Individuals in a Primary Care Setting Flags Putative Dementia Cases and Correlates Gastrointestinal Diseases with Poor Cognitive Performance. Dement Geriatr Cogn Disord. 2017;43(1-2):15-28. PMID: 27907913. **KQ2E8**
415. Rosell-Clari, V, Gonzalez, BV. Theory of Mind (ToM) and language: stimulating metalinguistic skills in people with dementia. Codas. 0(): 0. 2016. PMID: 27356191. https://dx.doi.org/10.1590/2317-1782/20162015295 **KQ4E5, KQ5E5**
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418. Sacco, G, Caillaud, C, et al. Exercise Plus Cognitive Performance over and above Exercise Alone in Subjects with Mild Cognitive Impairment. J Alzheimers Dis. 50(1): 19-25. 2015. https://dx.doi.org/10.3233/JAD-150194 **KQ4E2b, KQ5E2b**
419. Salva, A. Health and nutritional promotion program for patients with dementia (Nutrialz Study): design and baseline data. J Nutr Health Aging. 14(1): 78. 2010. **KQ4E5, KQ5E5**
420. Sanchez, MA, Lourenco, RA. Screening for dementia: Brazilian version of the Informant Questionnaire on Cognitive Decline on the Elderly and its psychometric properties. Geriatr Gerontol Int. 13(3): 687-93. 2013. PMID: 23186020. https://dx.doi.org/10.1111/j.1447-0594.2012.00966.x **KQ2E3a**
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https://dx.doi.org/10.1590/0101-60830000000066 **KQ4E3a, KQ5E3a**

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423. Savulich, G, Piercy, T, et al. Cognitive Training Using a Novel Memory Game on an iPad in Patients with Amnestic Mild Cognitive Impairment (aMCI). International Journal of Neuropsychopharmacology. 20(8): 624-633. 2017. PMID: 28898959. https://dx.doi.org/10.1093/ijnp/pyx040 **KQ4E2c, KQ5E2c**
424. Scharre DW, Chang SI, Nagaraja HN, et al. Digitally translated Self-Administered Gerocognitive Examination (eSAGE): relationship with its validated paper version, neuropsychological evaluations, and clinical assessments. Alzheimers Res Ther. 2017;9(1):44. PMID: 28655351. **KQ2E2d**
425. Scharre, DW, Chang, SI, et al. Self-administered Gerocognitive Examination (SAGE): a brief cognitive assessment Instrument for mild cognitive impairment (MCI) and early dementia. Alzheimer Dis Assoc Disord. 24(1): 64-71. 2010. PMID: 20220323. https://dx.doi.org/20220323 **KQ2E3c**
426. Schinka, JA, Robinson, DC, et al. Cognitive change checklist: psychometric characteristics in community-dwelling older adults. American Journal of Geriatric Psychiatry. 20(12): 1070-4. 2012. PMID: 23032479. https://dx.doi.org/10.1097/JGP.0b013e3182702c31 **KQ2E3c**
427. Schmid, AA, Spangler-Morris, C, et al. The Home-Based Occupational Therapy Intervention in the Alzheimer's Disease Multiple Intervention Trial (ADMIT). Occup Ther Ment Health. 31(1): 19-34. 2015. PMID: 26997685. https://dx.doi.org/10.1080/0164212X.2014.1002963 **KQ4E8, KQ5E8**
428. Schmitter-Edgecombe, M, Dyck, DG. Cognitive rehabilitation multi-family group intervention for individuals with mild cognitive impairment and their care-partners. Journal of the International Neuropsychological Society. 20(9): 897-908. 2014. PMID: 25222630. https://dx.doi.org/10.1017/S1355617714000782 **KQ4E7c, KQ5E7c**
429. Schneider, LS, Olin, JT, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 11 Suppl 2(): S22-32. 1997. PMID: 9236949. **KQ2E1**
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433. Sepe-Monti, Micaela, Vanacore, Nicola, et al. The Savvy Caregiver Program: A probe multicenter randomized controlled pilot trial in caregivers of patients affected by Alzheimer's disease. J Alzheimers Dis. 54(3): 1235-1246. 2016. https://dx.doi.org/10.3233/JAD-160235 **KQ4E7c, KQ5E7c**
434. Servello A, Ettorre E, Cacciafesta M. Improvement in behavioral and psychological symptoms of dementia by rivastigmine patch in a group of Italian elderly patients with Alzheimer's disease. Panminerva medica. 2017;59(3):275-7. PMID: 28665099. **KQ4E2c, KQ5E2c**
435. Shaaban, Juwita, Aziz, Aniza Abdul, et al. Validation of the Malay version of Rowland Universal Dementia Assessment Scale (M_RUDAS) among elderly attending primary care clinic. International Medical Journal. 20(5): 555-558. 2013. **KQ2E3a**
436. Shaik, MA, Xu, X, et al. The reliability and validity of the informant AD8 by comparison with a series of cognitive assessment tools in primary healthcare. Int Psychogeriatr. 28(3): 443-52. 2016.

PMID: 26489991. https://dx.doi.org/10.1017/S1041610215001702 **KQ2E5**

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438. Shelton, Jt, Lee, Jh, et al. Improving Prospective Memory in Healthy Older Adults and Individuals with Very Mild Alzheimer's Disease. J Am Geriatr Soc. 64(6): 1307-1312. 2016. PMID: Pubmed 27321610. https://dx.doi.org/10.1111/jgs.14134 **KQ4E2b, KQ5E2b**
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441. Silva, AR, Pinho, MS, et al. The Cognitive Effects of Wearable Cameras in Mild Alzheimer Disease - An Experimental Study. Curr Alzheimer Res. 14(12): 1270-1282. 2017. PMID: 28558637. https://dx.doi.org/10.2174/1567205014666170531083015 **KQ4E8, KQ5E8**
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445. Smith, K, Flicker, L, et al. The KICA Carer: informant information to enhance the Kimberley Indigenous Cognitive Assessment. Int Psychogeriatr. 28(1): 101-7. 2016. PMID: 26272042. https://dx.doi.org/10.1017/S1041610215001283 **KQ2E4a**
446. Smith, KE. Assessment and prevalence of dementia in Indigenous Australians. School of Primary, Aboriginal and Rural Health Care. Doctor of Philosophy in Medicine. 2008. PMID: None. **KQ2E4a**
447. Sobol, Na, Hoffmann, K, et al. Effect of aerobic exercise on physical performance in patients with Alzheimer's disease. Alzheimer's & dementia. 2016. https://dx.doi.org/10.1016/j.jalz.2016.05.004 **KQ4E5, KQ5E5**
448. Sogaard, R, Sorensen, J, et al. Early psychosocial intervention in Alzheimer's disease: cost utility evaluation alongside the Danish Alzheimer's Intervention Study (DAISY). BMJ Open. 4(1): e004105. 2014. PMID: 24435893. https://dx.doi.org/10.1136/bmjopen-2013-004105 **KQ4E5, KQ5E5**
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450. Sopina E, Sorensen J, Beyer N, et al. Cost-effectiveness of a randomised trial of physical activity in Alzheimer's disease: a secondary analysis exploring patient and proxy-reported health-related quality of life measures in Denmark. BMJ Open. 2017;7(6):e015217. PMID: 28615271. **KQ4E5, KQ5E5**
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program in the treatment of Alzheimer's disease: the Maximizing Independence in Dementia (MIND) study. Int J Geriatr Psychiatry. 24(7): 680-685. 2009. PMID: 19089875. **KQ4E6c, KQ5E6c**

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456. Streater, A, Spector, A, et al. Maintenance Cognitive Stimulation Therapy (CST) in practice: study protocol for a randomized controlled trial. Trials [Electronic Resource]. 13(): 91. 2012. PMID: 22735077. https://dx.doi.org/10.1186/1745-6215-13-91 **KQ4E5, KQ5E5**
457. Stubendorff, K, Larsson, V, et al. Treatment effect of memantine on survival in dementia with Lewy bodies and Parkinson's disease with dementia: a prospective study. BMJ Open. 4(7): e005158. 2014. PMID: 24993765. https://dx.doi.org/10.1136/bmjopen-2014-005158 **KQ4E4b, KQ5E4b**
458. Sukontapol C, Kemsen S, Chansirikarn S, et al. The effectiveness of a cognitive training program in people with mild cognitive impairment: A study in urban community. Asian journal of psychiatry. 2018;35:61-6. PMID: 29787954. **KQ4E3a, KQ5E3a**
459. Sumiyoshi T, Toyomaki A, Kawano N, et al. Reliability and validity of the California Verbal Learning Test-II - Japanese version. Psychiatry Clin Neurosci. 2017;71(6):417-8. PMID: 28317219. **KQ2E3b**
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462. Suttanon, P, Hill, KD, et al. Feasibility, safety and preliminary evidence of the effectiveness of a home-based exercise programme for older people with Alzheimer's disease: a pilot randomized controlled trial. Clin Rehabil. 27(5): 427-38. 2013. PMID: 23117349. https://dx.doi.org/10.1177/0269215512460877 **KQ4E6c, KQ5E6c**
463. Szczesniak, D, Wojtynska, R, et al. Test Your Memory (TYM) as a screening instrument in clinical practice - the Polish validation study. Aging Ment Health. 17(7): 863-8. 2013. PMID: 23557247. https://dx.doi.org/10.1080/13607863.2013.784957 **KQ2E2d**
464. Tanaka, S, Honda, S, et al. Comparison between group and personal rehabilitation for dementia in a geriatric health service facility: single-blinded randomized controlled study. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society. 17(3): 177-185. 2017. PMID: 27612310. https://dx.doi.org/10.1111/psyg.12212 **KQ4E3b, KQ5E3b**
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483. Valencia N, Lehrner J. Screening for dementia with the Vienna Visuo-Constructional Test 3.0 screening (VVT 3.0 screening). Neuropsychiatr. 2018. PMID: 29987508. **KQ2E2d**
484. van den Dungen, P, Moll van Charante, EP, et al. Case Finding of Mild Cognitive Impairment and Dementia and Subsequent Care; Results of a Cluster RCT in Primary Care. PLoS One. 11(6): e0156958. 2016. PMID: 27310616. https://dx.doi.org/10.1371/journal.pone.0156958 **KQ1E1**, **KQ3E1**
485. van Der Putt, R, Dineen, C, et al. Effectiveness of acetylcholinesterase inhibitors: diagnosis and severity as predictors of response in routine practice. Int J Geriatr Psychiatry. 21(8): 755-760. 2006. PMID: 16906631. **KQ5E2f**
486. Van Mierlo, LD, Meiland, FJ, et al. Evaluation of DEM-DISC, customized e-advice on health and social support services for informal carers and case managers of people with dementia; a cluster randomized trial. Int Psychogeriatr. 27(8): 1365-78. 2015. PMID: 25872457. https://dx.doi.org/10.1017/S1041610215000423 **KQ4E2b**
487. Van Mierlo, LD, Wouters, H, et al. Screening for Mild Cognitive Impairment and Dementia with Automated, Anonymous Online and Telephone Cognitive Self-Tests. J Alzheimers Dis. 56(1): 249-259. 2017. PMID: 27911296. https://dx.doi.org/10.3233/JAD-160566 **KQ2E3c**
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491. van Uffelen, JG, Hopman-Rock, M, et al. Protocol for Project FACT: a randomised controlled trial on the effect of a walking program and vitamin B supplementation on the rate of cognitive decline and psychosocial wellbeing in older adults with mild cognitive impairment [ISRCTN19227688]. BMC Geriatr. 5(): 18. 2005. PMID: 16375760. **KQ4E8, KQ5E8**
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496. Vidoni, EricD, Watts, AmberS, et al. Feasibility of a memory clinic-based physical activity prescription program. J Alzheimers Dis. 53(1): 161-170. 2016. https://dx.doi.org/10.3233/JAD-160158 **KQ4E2c, KQ5E2c**
497. Waelde, LC, Meyer, H, et al. Randomized Controlled Trial of Inner Resources Meditation for Family Dementia Caregivers. J Clin Psychol. 2017. PMID: 28263398. https://dx.doi.org/10.1002/jclp.22470 **KQ4E2b, KQ5E2b**
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499. Wang, CS, Pai, MC, et al. Montreal Cognitive Assessment and Mini-Mental State Examination performance in patients with mild-to-moderate dementia with Lewy bodies, Alzheimer's disease, and normal participants in Taiwan. Int Psychogeriatr. 25(11): 1839-48. 2013. PMID: 23919950. https://dx.doi.org/10.1017/S1041610213001245 **KQ2E2d**
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506. Whitebird, RR, Kreitzer, M, et al. Mindfulness-based stress reduction for family caregivers: a randomized controlled trial. Gerontologist. 53(4): 676-86. 2013. PMID: 23070934. https://dx.doi.org/10.1093/geront/gns126 **KQ4E2b**
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511. Wilkinson, D, Roman, G, et al. The long-term efficacy and tolerability of donepezil in patients with vascular dementia. Int J Geriatr Psychiatry. 25(3): 305-313. 2010. PMID: 19623601. **KQ5E2f**
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514. Wiloth, S, Werner, C, et al. Motor-cognitive effects of a computerized game-based training method in people with dementia: a randomized controlled trial. Aging Ment Health. 1-12. 2017. PMID: 28682124. https://dx.doi.org/10.1080/13607863.2017.1348472 **KQ4E5, KQ5E5**
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519. Wong, A, Fong, CH, et al. Computerized Cognitive Screen (CoCoSc): A Self-Administered Computerized Test for Screening for Cognitive Impairment in Community Social Centers. J Alzheimers Dis. 59(4): 1299-1306. 2017. PMID: 28731437. https://dx.doi.org/10.3233/JAD-170196 **KQ2E7b**
520. Wong A, Yiu S, Nasreddine Z, et al. Validity and reliability of two alternate versions of the Montreal Cognitive Assessment (Hong Kong version) for screening of Mild Neurocognitive Disorder. PLoS ONE [Electronic Resource]. 2018;13(5):e0196344. PMID: 29791452. **KQ2E2d**
521. Wray, Lo, Wade, M, et al. A program to improve detection of undiagnosed dementia in primary care and its association with healthcare utilization. American journal of geriatric psychiatry. 22(11): 1282-91. 2014. https://dx.doi.org/10.1016/j.jagp.2013.04.018 **KQ1E2a, KQ3E2a**
522. Yang, SY, Shan, CL, et al. The Effects of Aerobic Exercise on Cognitive Function of Alzheimer's Disease Patients. CNS Neurol Disord Drug Targets. 14(10): 1292-7. 2015. PMID: 26556080. **KQ4E3a, KQ5E3a**
523. Yatabe, Yusuke, Hashimoto, Mamoru, et al. Efficacy of increasing donepezil in mild to moderate Alzheimer's disease patients who show a diminished response to 5 mg donepezil: A preliminary study. Psychogeriatrics. 13(2): 88-93. 2013. https://dx.doi.org/10.1111/psyg.12004 **KQ4E2a, KQ5E2a**
524. Yeo S, Lee T, Sng W, et al. Effectiveness of a Personalized Brain-Computer Interface System for Cognitive Training in

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Healthy Elderly: a Randomized Controlled Trial. Journal of alzheimer's disease. 2018;66(1):127-38. PMID: 30248056. **KQ4E2c, KQ5E2c**

525. Yoon BK, Chin J, Kim JW, et al. Menopausal hormone therapy and mild cognitive impairment: a randomized, placebo-controlled trial. Menopause. 2018;25(8):870-6. PMID: 29846283. **KQ4E7c, KQ5E7c**
526. Yoon, DH, Kang, D, et al. Effect of elastic band-based high-speed power training on cognitive function, physical performance and muscle strength in older women with mild cognitive impairment. Geriatr Gerontol Int. 17(5): 765-772. 2017. PMID: 27396580. https://dx.doi.org/10.1111/ggi.12784 **KQ4E7c, KQ5E7c**
527. Young, DK, Kwok, TC, et al. A single blind randomized control trial on support groups for Chinese persons with mild dementia. Clin Interv Aging. 9(): 2105-12. 2014. PMID: 25587218. https://dx.doi.org/10.2147/CIA.S68687 **KQ4E2c, KQ5E2c**
528. Young DK. Multicomponent intervention combining a cognitive stimulation group and tai chi to reduce cognitive decline among community-dwelling older adults with probable dementia: A multi-center, randomized controlled trial. Dementia (London, England). 2018:1471301218814637. PMID: 30486656. **KQ4E2c, KQ5E2c**
529. Young DK, Ng PY, Kwok T, et al. The effects of an expanded cognitive stimulation therapy model on the improvement of cognitive ability of elderly with mild stage Dementia living in a community - a randomized waitlist controlled trial. Aging Ment Health. 2018:1-8. PMID: 29781725. **KQ4E2c, KQ5E2c**
530. Young KW. A Randomized Control Study on Psycho-Education Group on Improving Health-Related Quality of Life of Chinese Persons with Major Neurocognitive Disorder. Clinical Gerontologist. 2016;39(5):449-67. PMID: 29471772. **KQ4E2c, KQ5E2c**
531. Young KW, Ng P, Kwok T, et al. The effects of holistic health group interventions on improving the cognitive ability of persons with mild cognitive impairment: a randomized controlled trial. Clinical Interventions In Aging. 2017;12:1543-52. PMID: 29026292. **KQ4E2c, KQ5E2c**
532. Zainal, NH, Silva, E, et al. Psychometric Properties of Alzheimer's Disease Assessment Scale-Cognitive Subscale for Mild Cognitive Impairment and Mild Alzheimer's Disease Patients in an Asian Context. Ann Acad Med Singapore. 45(7): 273-83. 2016. PMID: 27523508. **KQ2E2d**
533. Zauszniewski, JA, Lekhak, N, et al. Preliminary Evidence for Effectiveness of Resourcefulness Training in Women Dementia Caregivers. J Fam Med. 3(5). 2016. PMID: 27500286. **KQ4E2c, KQ5E2c**
534. Zhang, J, Wang, Z, et al. The effects of CCRC on cognition and brain activity in aMCI patients: a pilot placebo controlled BOLD fMRI study. Curr Alzheimer Res. 11(5): 484-93. 2014. PMID: Pubmed 24801219. **KQ4E6b**, **KQ5E6b**
535. Zhang, N, Wei, C, et al. The Effect of Memantine on Cognitive Function and Behavioral and Psychological Symptoms in Mild-to-Moderate Alzheimer's Disease Patients. Dement Geriatr Cogn Disord. 40(1-2): 85-93. 2015. PMID: 26066622. https://dx.doi.org/10.1159/000430808 **KQ4E3a, KQ5E3a**
536. Zhang, Y-P, Miao, R, et al. Effects of DHA Supplementation on Hippocampal Volume and Cognitive Function in Older Adults with Mild Cognitive Impairment: a 12-Month Randomized, Double-Blind, Placebo-Controlled Trial. J Alzheimers Dis. 55(2): 497-507. 2017. https://dx.doi.org/10.3233/JAD-160439 **KQ4E3a, KQ5E3a**
537. Zhao, Q, Guo, Q, et al. The Shape Trail Test: application of a new variant of the Trail making test. PLoS ONE [Electronic Resource]. 8(2): e57333. 2013. PMID: 23437370. https://dx.doi.org/10.1371/journal.pone.0057333 **KQ2E3a**
538. Zhao, Q, Lv, Y, et al. Short-term delayed recall of auditory verbal learning test is equivalent to long-term delayed recall for identifying amnestic mild cognitive impairment. PLoS ONE [Electronic Resource]. 7(12): e51157. 2012. PMID: 23236445. https://dx.doi.org/10.1371/journal.pone.0051157 **KQ2E3a**

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539. Zieschang, T, Schwenk, M, et al. Falls and Physical Activity in Persons With Mild to Moderate Dementia Participating in an Intensive Motor Training: Randomized Controlled Trial. Alzheimer Dis Assoc Disord. 2017. PMID: 28628488. https://dx.doi.org/10.1097/wad.0000000000000201 **KQ4E6c, KQ5E6c**
540. Zhu Y, Wu H, Qi M, et al. Effects of a specially designed aerobic dance routine on mild cognitive impairment. Clinical Interventions In Aging. 2018;13:1691-700. PMID: 30237705. **KQ4E3a, KQ5E3a**
541. Zwingmann I, Michalowsky B, Esser A, et al. Identifying Unmet Needs of Family Dementia Caregivers: Results of the Baseline Assessment of a Cluster-Randomized Controlled Intervention Trial. Journal of Alzheimer's Disease. 2018;19:19. PMID: 30584136. **KQ4E2a, KQ5E2a**

Appendix E Table 1. AChEIs and Memantine: Detailed Results for Global Cognitive Function Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Donepezil	Black, 2003[184] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	6	20.9‡ (0.7)§	186	NR	-1.52‖ (0.40)§	20.1‡ (0.7)§	188	NR	0.72‖ (0.40)§	NR, <0.001
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG2	6	21.2‡ (0.8)§	185	NR	-0.96‖ (0.39)§	20.1‡ (0.7)§	188	NR	0.72‖ (0.40)§	NR, <0.01
Donepezil		Dem	MMSE (0-30)	IG1	6	21.8‡ (0.3)§	195	NR	1.49‖ (0.20)§	21.7‡ (0.3)§	194	NR	0.39‖ (0.23)§	NR, <0.001
Donepezil		Dem	MMSE (0-30)	IG2	6	21.9‡ (0.3)§	196	NR	1.04‖ (0.21)§	21.7‡ (0.3)§	194	NR	0.39‖ (0.23)§	NR, <0.05
Donepezil	Burns, 1999[185] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	NR	202	NR	-1.90‖ (0.31)§	NR	219	NR	0.37‖ (0.30)§	NR, <0.0001
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG1	4	NR	202	NR	-1.70‖ (0.37)§	NR	219	NR	1.31‖ (0.38)§	NR, <0.0001
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG1	6	NR	273	NR	-1.27‖ (0.35)§	NR	274	NR	1.66‖ (0.36)§	LSM Change=-2.9, <0.0001
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG2	3	NR	211	NR	-1.54‖ (0.29)§	NR	219	NR	0.37‖ (0.30)§	NR, <0.0001
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG2	4	NR	211	NR	-0.58‖ (0.35)§	NR	219	NR	1.31‖ (0.38)§	NR, 0.0002
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG2	6	NR	271	NR	0.18‖ (0.35)§	NR	274	NR	1.66‖ (0.36)§	LSM Change=-1.5, 0.0021
Donepezil	Doody, 2009[186] Fair	MCI	ADAS-Cog 13 (0-89)	IG1	11	18.3 (6.6)	379	NR	-1.0 (0.4)§	18.2 (7.0)	378	NR	-0.13 (0.4)§	MDC (SE)=-0.9 (0.37), 0.01
Donepezil		MCI	MMSE (0-30)	IG1	11	27.5 (1.9)	379	NR	0.1 (0.1)§	27.4 (1.9)	378	NR	0.0 (0.2)§	NS
Donepezil	Feldman, 2001[187] Fair-Good	Dem	MMSE (0-30)	IG1	3	11.72 (0.35)§	127	NR	1.79‖ (0.35)§	11.97 (0.34)§	132	NR	0.23‖ (0.34)§	NR, 0.0004
Donepezil		Dem	MMSE (0-30)	IG1	6	11.72 (0.35)§	131	NR	1.34‖ (0.34)§	11.97 (0.34)§	139	NR	-0.42‖ (0.34)§	MDC=1.79, <0.0001
Donepezil	Holmes, 2004[188] Fair-Good	Dem	MMSE (0-30)	IG1	6	21.1 (0.9)§	41	NR	-0.1 (0.6)§	20.8 (0.6)§	55	NR	1.8 (0.5)§	NR, 0.02
Donepezil	Ikeda, 2015*[189] Fair	Dem	MMSE (0-30)	IG1	3	20.3 (4.8)	49	NR	2.2 (0.4)§	20.3 (4.2)	44	NR	0.6 (0.5)§	MDC (95% CI)=1.6 (0.3, 2.8), 0.016
Donepezil		Dem	MMSE (0-30)	IG2	3	20.6 (4.1)	43	NR	1.4 (0.5)§	20.3 (4.2)	44	NR	0.6 (0.5)§	MDC (95% CI)=0.8 (-0.5, 2.1), 0.232
Donepezil	Krishnan, 2003[190] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	26.51 (12.13)	31	NR	-2.06‖ (NR)	26.44 (12.29)	30	NR	1.22‖ (NR)	NR, <0.007
Donepezil	Krishnan, 2003[190] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	4	26.51 (12.13)	30	NR	-1.72‖ (NR)	26.44 (12.29)	29	NR	1.60‖ (NR)	NR, <0.04
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG1	6	26.51 (12.13)	34	NR	0.01‖ (NR)	26.44 (12.29)	32	NR	3.2‖ (NR)	NR, <0.04

Appendix E Table 1. AChEIs and Memantine: Detailed Results for Global Cognitive Function Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Donepezil	Mazza, 2006[191] Fair-Good	Dem	MMSE (0-30)	IG1	6	18.55 (3.47)	25	NR	1.2 (-3.6, 1.2)¶	18.80 (3.63)	26	NR	-0.25 (-2.17, 2.67)¶	MDC (95% CI)=1.2 (-1.2, 3.6), 0.06
Donepezil	Mori, 2012[193] Fair	Dem	MMSE (0-30)	IG1	3	19.8 (4.4)	36	NR	2.0 (3.3)	18.3 (4.7)	31	NR	-0.4 (2.7)	MDC (95% CI)=2.4 (0.9, 3.9), <0.001
Donepezil		Dem	MMSE (0-30)	IG2	3	19.8 (4.4)	32	NR	3.4 (3.2)	18.3 (4.7)	31	NR	-0.4 (2.7)	MDC (95% CI)=3.8 (2.3, 5.3), <0.001
Donepezil		Dem	MMSE (0-30)	IG3	3	20.4 (4.1)	35	NR	1.6 (3.8)	18.3 (4.7)	31	NR	-0.4 (2.7)	MDC (95% CI)=2.0 (0.4, 3.7), 0.013
Donepezil	Petersen, 2005[194] Fair	MCI	ADAS-Cog 11 (0-70)	IG1	6	11.28 (4.5)	NR	NR	-0.61 (3.79)	11.03 (4.2)	NR	NR	-0.13 (3.34)	NR
Donepezil		MCI	ADAS-Cog 11 (0-70)	IG1	12	11.28 (4.5)	NR	NR	0.17 (3.73)	11.03 (4.2)	NR	NR	0.61 (4.10)	NR
Donepezil		MCI	ADAS-Cog 11 (0-70)	IG1	18	11.28 (4.5)	NR	NR	1.08 (4.37)	11.03 (4.2)	NR	NR	1.29 (4.71)	NR
Donepezil		MCI	ADAS-Cog 11 (0-70)	IG1	24	11.28 (4.5)	NR	NR	1.22 (4.79)	11.03 (4.2)	NR	NR	1.49 (5.07)	NR
Donepezil		MCI	ADAS-Cog 11 (0-70)	IG1	30	11.28 (4.5)	NR	NR	2.71 (5.21)	11.03 (4.2)	NR	NR	2.98 (5.62)	NR
Donepezil		MCI	ADAS-Cog 11 (0-70)	IG1	36	11.28 (4.5)	161	NR	3.68 (5.95)	11.03 (4.2)	193	NR	3.74 (6.97)	NR
Donepezil		MCI	ADAS-Cog 13 (0-85)	IG1	6	17.72 (6.2)	NR	NR	-1.23 (4.74)	17.40 (6.0)	NR	NR	-0.09 (4.38)	NR
Donepezil		MCI	ADAS-Cog 13 (0-85)	IG1	12	17.72 (6.2)	NR	NR	-0.55 (5.20)	17.40 (6.0)	NR	NR	0.60 (4.96)	NR
Donepezil		MCI	ADAS-Cog 13 (0-85)	IG1	18	17.72 (6.2)	NR	NR	0.03 (5.64)	17.40 (6.0)	NR	NR	0.99 (6.07)	NR
Donepezil		MCI	ADAS-Cog 13 (0-85)	IG1	24	17.72 (6.2)	NR	NR	0.35 (6.23)	17.40 (6.0)	NR	NR	1.02 (6.27)	NR
Donepezil	Petersen, 2005[194] Fair	MCI	ADAS-Cog 13 (0-85)	IG1	30	17.72 (6.2)	NR	NR	2.05 (6.74)	17.40 (6.0)	NR	NR	2.65 (7.02)	NR
Donepezil		MCI	ADAS-Cog 13 (0-85)	IG1	36	17.72 (6.2)	161	NR	3.12 (7.39)	17.40 (6.0)	193	NR	3.72 (8.54)	NR
Donepezil		MCI	MMSE (0-30)	IG1	6	27.25 (1.8)	NR	NR	0.06 (2.03)	27.35 (1.8)	NR	NR	-0.36 (2.02)	NR
Donepezil		MCI	MMSE (0-30)	IG1	12	27.25 (1.8)	NR	NR	-0.31 (2.25)	27.35 (1.8)	NR	NR	-0.80 (2.34)	NR
Donepezil		MCI	MMSE (0-30)	IG1	18	27.25 (1.8)	NR	NR	-0.52 (2.46)	27.35 (1.8)	NR	NR	-1.02 (2.61)	NR
Donepezil		MCI	MMSE (0-30)	IG1	24	27.25 (1.8)	NR	NR	-0.98 (2.54)	27.35 (1.8)	NR	NR	-1.49 (2.90)	NR

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Medication	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Donepezil		MCI	MMSE (0-30)	IG1	30	27.25 (1.8)	NR	NR	-1.47 (3.04)	27.35 (1.8)	NR	NR	-1.77 (3.24)	NR
Donepezil		MCI	MMSE (0-30)	IG1	36	27.25 (1.8)	161	NR	-2.31 (3.72)	27.35 (1.8)	193	NR	-2.75 (4.04)	NR
Donepezil	Rogers, 1996[196] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	29.1 (NR)	38	NR	-2.5 (-8.0, 7.0)#	27.2 (NR)	40	NR	0.7 (-7.0, 14.5)#	NR, <0.01
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG2	3	29.2 (NR)	40	NR	-1.4 (-12.0, 11.0)#	27.2 (NR)	40	NR	0.7 (-7.0, 14.5)#	NR, <0.05
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG3	3	26.6 (NR)	41	NR	-0.9 (-11.3, 12.0)#	27.2 (NR)	40	NR	0.7 (-7.0, 14.5)#	NS
Donepezil		Dem	MMSE (0-30)	IG1	3	18.0 (NR)	38	NR	2.0 (-1.0, 7.0)#	18.2 (NR)	40	NR	1.2 (-6.0, 8.0)#	NS
Donepezil		Dem	MMSE (0-30)	IG2	3	18.6 (NR)	40	NR	0.9 (-7.0, 5.0)#	18.2 (NR)	40	NR	1.2 (-6.0, 8.0)#	NS
Donepezil		Dem	MMSE (0-30)	IG3	3	19.6 (NR)	41	NR	0.6 (-4.0, 7.0)#	18.2 (NR)	40	NR	1.2 (-6.0, 8.0)#	NS
Donepezil	Rogers, 1998[195] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	26.4 (0.89)§	155	NR	-2.7‖ (0.43)§	25.3 (0.87)§	150	NR	0.4‖ (0.43)§	MDC (95% CI)=-3.1 (-4.22, -1.92), <0.001
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG2	3	26.4 (0.92)§	156	NR	-2.1‖ (0.43)§	25.3 (0.87)§	150	NR	0.4‖ (0.43)§	MDC (95% CI)=-2.5 (-3.59, -1.29), <0.001
Donepezil		Dem	MMSE (0-30)	IG1	3	19.35 (0.40)§	156	NR	1.3‖ (0.24)§	19.80 (0.35)§	150	NR	0.04‖ (0.25)§	MDC (95% CI)=1.3 (0.65, 1.97), <0.001
Donepezil		Dem	MMSE (0-30)	IG2	3	19.39 (0.39)§	156	NR	1.0‖ (0.25)§	19.80 (0.35)§	150	NR	0.04‖ (0.25)§	MDC (95% CI)=1.0 (0.33, 1.65), <0.004
Donepezil	Salloway, 2004[197] Fair-Good	MCI	ADAS-Cog 13 (0-85)	IG1	6	20.0 (6.2)	130	NR	-3.1 (0.5)§	19.5 (6.9)	132	NR	-1.2 (0.5)§	NR, 0.006
Donepezil		MCI	ADAS-Cog 13 (D)	IG1	6	NA	130	105 (80.8)**	NR	NA	132	86 (65.2)**	NR	NR
Donepezil		MCI	ADAS-Cog 13 (D)	IG1	6	NA	130	65 (50.0)††	NR	NA	132	42 (31.8)††	NR	NR
Donepezil		MCI	ADAS-Cog 13 (D)	IG1	6	NA	130	29 (22.3)‡‡	NR	NA	132	16 (12.1)‡‡	NR	NR
Donepezil	Seltzer, 2004[198] Fair-Good	Dem	ADAS-Cog 13 (0-85)	IG1	3	21.0 (7.9)	79	NR	-1.52 (0.63)§	21.3 (6.8)	51	NR	0.39 (0.68)§	NR, 0.03
Donepezil		Dem	ADAS-Cog 13 (0-85)	IG1	4	21.0 (7.9)	70	NR	-1.32 (0.68)§	21.3 (6.8)	49	NR	0.29 (0.65)§	NR, NR

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Medication	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Donepezil		Dem	ADAS-Cog 13 (0-85)	IG1	6	21.0 (7.9)	91	NR	-1.64 (0.50)§	21.3 (6.8)	55	NR	0.59 (0.64)§	MDC=-2.3, 0.001
Donepezil		Dem	ADAS-Cog 13 (D)	IG1	6	NA	67	25 (37.3)††	NR	NA	45	7 (15.6)††	NR	NR, 0.02
Donepezil		Dem	MMSE (0-30)	IG1	3	24.1 (1.7)	79	NR	1.60 (0.37)§	24.3 (1.3)	51	NR	0.39 (0.38)§	NR, 0.04
Donepezil		Dem	MMSE (0-30)	IG1	6	24.1 (1.7)	91	NR	1.34 (0.36)§	24.3 (1.3)	55	NR	0.09 (0.42)§	MDC=1.8, 0.002
Donepezil	Tune, 2003[199] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	21.86 (6.59)	14	NR	-3.98‖ (3.46)	21.81 (10.00)	13	NR	-2.95‖ (3.40)	MDC (95% CI)=NR, (-3.75, 1.69), 0.459
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG1	6	21.86 (6.59)	14	NR	-3.65‖ (5.03)	21.81 (10.00)	13	NR	-1.56‖ (2.07)	MDC (95% CI)=NR, (-5.18, 1.00), 0.186
Donepezil	Wilkinson, 2003[200] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	20.6‡ (0.7)§	172	NR	-2.97‖ (0.41)§	18.8‡ (0.7)§	167	NR	-0.91‖ (0.38)§	NR, <0.001
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG1	4	20.6‡ (0.7)§	163	NR	-2.62‖ (0.48)§	18.8‡ (0.7)§	160	NR	-0.16‖ (0.44)§	NR, <0.001
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG1	6	20.6‡ (0.7)§	194	NR	-2.19‖ (0.44)§	18.8‡ (0.7)§	180	NR	-0.10‖ (0.39)§	NR, <0.001
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG2	3	20.8‡ (0.7)§	183	NR	-2.62‖ (0.35)§	18.8‡ (0.7)§	167	NR	-0.91‖ (0.36)§	NR, <0.001
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG2	4	20.8‡ (0.7)§	173	NR	-2.18‖ (0.35)§	18.8‡ (0.7)§	160	NR	-0.16‖ (0.38)§	NR, <0.001
Donepezil		Dem	ADAS-Cog 11 (0-70)	IG2	6	20.8‡ (0.7)§	199	NR	-1.75‖ (0.33)§	18.8‡ (0.7)§	180	NR	-0.10‖ (0.39)§	NR, <0.01
Donepezil		Dem	MMSE (0-30)	IG1	3	21.5‡ (0.3)§	179	NR	1.66‖ (0.17)§	22.2‡ (0.3)§	174	NR	0.29‖ (0.24)§	NR, <0.001
Donepezil	Wilkinson, 2003[200] Fair-Good	Dem	MMSE (0-30)	IG1	4	21.5‡ (0.3)§	169	NR	1.47‖ (0.23)§	22.2‡ (0.3)§	166	NR	0.62‖ (0.23)§	NR, <0.05
Donepezil		Dem	MMSE (0-30)	IG1	6	21.5‡ (0.3)§	203	NR	1.38‖ (0.23)§	22.2‡ (0.3)§	188	NR	0.23‖ (0.24)§	NR, <0.001
Donepezil		Dem	MMSE (0-30)	IG2	3	21.8‡ (0.3)§	185	NR	1.39‖ (0.23)§	22.2‡ (0.3)§	174	NR	0.29‖ (0.22)§	NR, <0.001
Donepezil		Dem	MMSE (0-30)	IG2	4	21.8‡ (0.3)§	175	NR	1.57‖ (0.21)§	22.2‡ (0.3)§	166	NR	0.62‖ (0.23)§	NR, <0.01
Donepezil		Dem	MMSE (0-30)	IG2	6	21.8‡ (0.3)§	202	NR	1.38‖ (0.22)§	22.2‡ (0.3)§	188	NR	0.23‖ (0.24)§	NR, <0.001
Donepezil	Winblad, 2001[201] Fair-Good	Dem	MMSE (0-30)	IG1	3	19.37 (4.37)	127	NR	0.69‖ (0.27)§	12.26 (4.54)	128	NR	-0.12‖ (0.29)§	NR, 0.053

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Medication	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Donepezil		Dem	MMSE (0-30)	IG1	6	19.37 (4.37)	121	NR	0.43‖ (0.34)§	12.26 (4.54)	120	NR	-1.05‖ (0.30)§	NR, <0.001
Donepezil		Dem	MMSE (0-30)	IG1	8	19.37 (4.37)	104	NR	0.02‖ (0.40)§	12.26 (4.54)	105	NR	-1.12‖ (0.39)§	NR, 0.019
Donepezil		Dem	MMSE (0-30)	IG1	12	19.37 (4.37)	135	NR	-0.49‖ (0.34)§	12.26 (4.54)	137	NR	-2.19‖ (0.25)§	NR, <0.001
Galantamine	Auchus, 2007[202] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	6	22.9 (9.5)	388	NR	-1.7 (6.0)	22.5 (9.5)	379	NR	-0.3 (6.4)	NR, 0.001
Galantamine	Brodaty, 2005[203] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	27.3 (0.55)§	296	NR	-2.5 (0.30)§	26.1 (0.54)§	296	NR	0.2 (0.31)§	NR
Galantamine		Dem	ADAS-Cog 11 (0-70)	IG1	6	27.3 (0.55)§	296	NR	-1.6 (0.36)§	26.1 (0.54)§	296	NR	1.2 (0.33)§	MDC (95% CI)= NR, (-3.70, -1.86), <0.01
Galantamine		Dem	ADAS-Cog 11 (0-70)	IG2	3	26.3 (0.54)§	290	NR	-2.0 (0.31)§	26.1 (0.54)§	296	NR	0.2 (0.31)§	NR
Galantamine		Dem	ADAS-Cog 11 (0-70)	IG2	6	26.3 (0.54)§	291	NR	-1.3 (0.31)§	26.1 (0.54)§	296	NR	1.2 (0.33)§	MDC (95% CI)= NR, (-3.34, -1.49), <0.001
Galantamine	Erkinjuntti, 2002[204] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	6	22.3 (8.8)	290	NR	-1.7 (0.4)§	24.1 (9.9)	162	NR	1.0 (0.5)§	MDC=-2.7, <0.0001
Galantamine		Dem	ADAS-Cog 11 (0-70)	IG1 (AD)	6	NR	152	NR	-1.0 (0.46)§	NR	87	NR	1.8 (0.60)§	MDC (95% CI)=-2.7 (-4.16, -1.17), 0.0005
Galantamine		Dem	ADAS-Cog 11 (0-70)	IG1 (VaD)	6	NR	121	NR	-2.4 (0.59)§	NR	67	NR	-0.4 (0.78)§	MDC (95% CI)=-1.9 (-3.88, 0.08), 0.06
Galantamine		Dem	ADAS-Cog 11 (D)	IG1	6	NA	290	102 (35.2)††	NR	NA	162	36 (22.2)††	NR	NR, 0.005
Galantamine		Dem	ADAS-Cog 13 (0-85)	IG1	6	NR	290	NR	-2.4 (0.4)§	NR	162	NR	0.9 (0.6)§	MDC=-3.2, <0.0001
Galantamine	Hager, 2014*[206] Fair	Dem	MMSE (0-30)	IG1	6	19.0 (4.12)	873	NR	0.15 (2.73)	19.0 (4.04)	888	NR	-0.28 (2.94)	NR, <0.001
Galantamine		Dem	MMSE (0-30)	IG1	12	19.0 (4.12)	874	NR	-0.51 (0.11)§	19.0 (4.04)	891	NR	-1.09 (0.12)§	NR, <0.05
Galantamine		Dem	MMSE (0-30)	IG1	18	19.0 (4.12)	874	NR	-1.07 (0.13)§	19.0 (4.04)	891	NR	-1.74 (0.13)§	NR, <0.05
Galantamine		Dem	MMSE (0-30)	IG1	24	19.0 (4.12)	874	NR	-1.41 (0.12)§	19.0 (4.04)	891	NR	-2.14 (0.13)§	NR, <0.001
Galantamine	Raskind, 2000[206] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	6	24.8 (0.7)§	202	NR	1.9 (0.36)§	25.7 (0.8)§	207	NR	2.0 (0.45)§	NR, <0.001
Galantamine		Dem	ADAS-Cog 11 (0-70)	IG2	6	25.8 (0.8)§	197	NR	-1.4 (0.44)§	25.7 (0.8)§	207	NR	2.0 (0.45)§	NR, <0.001

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Galantamine	Rockwood, 2001[208] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	25.6 (0.65)§	239	NR	-1.1 (0.33)§	24.7 (0.85)§	120	NR	0.6 (0.45)§	NR, <0.01
Galantamine		Dem	ADAS-Cog 11 (0-70)	IG1	3	NA	239	72 (30.1)	NR	NA	120	27 (22.5)	NR	NS
Galantamine	Rockwood, 2006[207] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	4	24.2 (6.4)	62	NR	-1.64 (-2.94, -0.27)¶	27.9 (8.4)	65	NR	0.29 (-1.02, 1.65)¶	NR, 0.04
Galantamine	Tariot, 2000[209] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	5	29.0 (0.7)§	253	NR	-1.4 (0.39)§	29.4 (0.6)§	255	NR	1.7 (0.39)§	NR, <0.001
Galantamine		Dem	ADAS-Cog 11 (D)	IG1	5	NA	211	78 (37.0)††	NR	NA	225	44 (19.6)††	NR	NR, <0.001
Galantamine		Dem	ADAS-Cog 11 (D)	IG1	5	NA	211	56 (26.5)‡‡	NR	NA	225	19 (8.4)‡‡	NR	NR, <0.01
Galantamine		Dem	ADAS-Cog 11 (0-70)	IG2	5	29.4 (0.7)§	253	NR	-1.4 (0.35)§	29.4 (0.6)§	255	NR	1.7 (0.39)§	NR, <0.001
Galantamine		Dem	ADAS-Cog 11 (D)	IG2	5	NA	253	40 (15.8)††	NR	NA	255	19 (7.4)††	NR	NR, <0.01
Galantamine		Dem	ADAS-Cog 11 (D)	IG2	5	NA	208	74 (35.6)‡‡	NR	NA	225	44 (19.6)‡‡	NR	NR, <0.001
Galantamine		Dem	ADAS-Cog 11 (0-70)	IG3	5	27.8 (0.9)§	126	NR	0.4 (0.52)§	29.4 (0.6)§	255	NR	1.7 (0.39)§	NS
Galantamine	Wilcock, 2000[210] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	6	25.4 (9.4)	220	NR	-0.5 (0.38)§	24.7 (9.3)	215	NR	2.4 (0.41)§	MDC (95% CI)=-2.9 (-4.1, -1.6), <0.001
Galantamine		Dem	ADAS-Cog 11 (D)	IG1	6	NA	220	138 (62.7)**	NR	NA	215	88 (40.9)**	NR	PD (95% CI)=21.5 (12.0, 31.0), <0.001
Galantamine		Dem	ADAS-Cog 11 (D)	IG1	6	NA	220	64 (29.1)††	NR	NA	215	32 (14.9)††	NR	PD (95% CI)=14.0 (6.0, 22.0), <0.001
Galantamine	Wilcock, 2000[210] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG2	6	26.2 (10.4)	217	NR	-0.8 (0.43)§	24.7 (9.3)	215	NR	2.4 (0.41)§	MDC (95% CI)=-3.1 (-4.4, -1.9), <0.001
Galantamine		Dem	ADAS-Cog 11 (D)	IG2	6	NA	217	130 (59.9)**	NR	NA	215	88 (40.9)**	NR	PD (95% CI)=19.5 (10.0, 29.0), <0.001
Galantamine		Dem	ADAS-Cog 11 (D)	IG2	6	NA	217	70 (32.2)††	NR	NA	215	32 (14.9)††	NR	PD (95% CI)=17.0 (9.0, 25.0), <0.001
Galantamine	Wilkinson, 2001[211] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	26.7 (1.1)§	55	NR	-1.4 (0.9)§	26.9 (1.0)§	82	NR	1.6 (0.7)§	MDC=NR, <0.01
Galantamine		Dem	ADAS-Cog 11 (0-70)	IG2	3	25.7 (1.1)§	51	NR	-0.7 (0.7)§	26.9 (1.0)§	82	NR	1.6 (0.7)§	MDC=NR, 0.08
Galantamine		Dem	ADAS-Cog 11 (0-70)	IG3	3	26.0 (0.9)§	81	NR	-0.1 (0.7)§	26.9 (1.0)§	82	NR	1.6 (0.7)§	MDC=NR, NS
Rivastigmine		Dem	MMSE (0-30)	IG1	3	NR	103	NR	0.3 (3.1)	NR	117	NR	-0.0 (2.6)	NR

Appendix E Table 1. AChEIs and Memantine: Detailed Results for Global Cognitive Function Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Rivastigmine	Agid, 1998[212] Fair-Good	Dem	MMSE (0-30)	IG2	3	NR	111	NR	0.0 (3.3)	NR	117	NR	-0.0 (2.6)	NR
Rivastigmine	Ballard, 2008[213] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	6	23.0 (9.9)	360	NR	-0.7 (0.38)§	23.7 (9.8)	338	NR	0.4 (0.38)§	MDC=-1.0, 0.029
Rivastigmine		Dem	MMSE (0-30)	IG1	6	19.2 (4.1)	360	NR	0.4 (0.38)§	19.2 (3.9)	338	NR	-0.2 (0.18)§	MDC=0.6, 0.007
Rivastigmine	Corey-Bloom, 1998[214] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	22.3 (NR)	169	NR	-1.0 (NR)	21.7 (NR)	216	NR	2.3 (NR)	NR, <0.001
Rivastigmine		Dem	ADAS-Cog 11 (0-70)	IG1	4	22.3 (NR)	157	NR	-0.6 (NR)	21.7 (NR)	201	NR	3.5 (NR)	NR, <0.001
Rivastigmine		Dem	ADAS-Cog 11 (0-70)	IG1	6	22.3 (NR)	231	NR	-0.31 (-1.08, 0.49)¶	21.7 (NR)	234	NR	4.09 (3.32, 4.86)¶	MDC=-4.40, <0.001
Rivastigmine		Dem	ADAS-Cog 11 (D)	IG1	6	NA	145	81 (55.9)**	NR	NA	192	52 (27.1)**	NR	NS
Rivastigmine		Dem	ADAS-Cog 11 (0-70)	IG2	3	22.4 (NR)	223	NR	1.4 (NR)	21.7 (NR)	216	NR	2.3 (NR)	NR
Rivastigmine		Dem	ADAS-Cog 11 (0-70)	IG2	4	22.4 (NR)	208	NR	1.8 (NR)	21.7 (NR)	201	NR	3.5 (NR)	NR, <0.05
Rivastigmine		Dem	ADAS-Cog 11 (0-70)	IG2	6	22.4 (NR)	233	NR	2.36 (1.59, 3.13)¶	21.7 (NR)	234	NR	4.09 (3.32, 4.86)¶	NR
Rivastigmine		Dem	MMSE (0-30)	IG1	6	19.62 (NR)	145	NR	0.30 (NR)	20.00 (NR)	192	NR	-0.79 (NR)	NR, <0.05
Rivastigmine		Dem	MMSE (0-30)	IG2	6	19.5 (NR)	194	NR	-0.34 (NR)	20.0 (NR)	192	NR	-0.79 (NR)	NR
Rivastigmine	Feldman, 2007[215] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	6	28.1 (12.5)	227	NR	-0.2 (7.3)	28.5 (12.3)	220	NR	2.8 (7.2)	MDC=-2.9, <0.001
Rivastigmine		Dem	ADAS-Cog 11 (D)	IG1	3	NA	227	68 (30.0)††	NR	NA	220	36 (16.4)††	NR	NR, ≤0.001
Rivastigmine		Dem	ADAS-Cog 11 (D)	IG1	4	NA	227	75 (33.0)††	NR	NA	220	28 (12.7)††	NR	NR, ≤0.001
Rivastigmine		Dem	ADAS-Cog 11 (D)	IG1	6	NA	227	52 (22.9)††	NR	NA	220	28 (12.7)††	NR	NR, <0.05
Rivastigmine		Dem	ADAS-Cog 11 (0-70)	IG2	6	27.7 (12.3)	228	NR	1.2 (7.2)	28.5 (12.3)	220	NR	2.8 (7.2)	MDC=-1.6, 0.019
Rivastigmine		Dem	ADAS-Cog 11 (D)	IG2	3	NA	228	53 (23.2)††	NR	NA	220	36 (16.4)††	NR	NR, <0.05
Rivastigmine		Dem	ADAS-Cog 11 (D)	IG2	4	NA	228	57 (25.0)††	NR	NA	220	28 (12.7)††	NR	NR, ≤0.001

Appendix E Table 1. AChEIs and Memantine: Detailed Results for Global Cognitive Function Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Rivastigmine		Dem	ADAS-Cog 11 (D)	IG2	6	NA	228	41 (18.0)††	NR	NA	220	28 (12.7)††	NR	NS
Rivastigmine		Dem	MMSE (0-30)	IG1	6	18.1 (4.7)	277	NR	0.3 (3.6)	18.6 (4.7)	220	NR	-1.4 (3.6)	NR
Rivastigmine		Dem	MMSE (0-30)	IG2	6	18.8 (4.7)	228	NR	-0.6 (3.6)	18.6 (4.7)	220	NR	-1.4 (3.6)	NR
Rivastigmine	McKeith, 2000[216] Fair-Good	Dem	MMSE (0-30)	IG1	5	17.9 (4.7)	41	NR	1.5 (NR)	17.8 (4.4)	51	NR	-0.1 (NR)	NR, 0.072
Rivastigmine	Mok, 2007[217] Fair	Dem	MMSE (0-30)	IG1	6	13.0 (4.2)	20	13.6 (5.8)	NR	13.6 (6.0)	19	13.5 (6.8)	NR	NR, 0.563
Rivastigmine	Rosler, 1999[218] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	NR	191	NR	-1.85 (NR)	NR	226	NR	-0.08 (NR)	NR, <0.05
Rivastigmine		Dem	ADAS-Cog 11 (0-70)	IG1	4	NR	179	NR	-0.90 (NR)	NR	218	NR	1.21 (NR)	NR, <0.05
Rivastigmine		Dem	ADAS-Cog 11 (0-70)	IG1	6	NR	199	NR	-0.83 (-1.79, 0.19)¶	NR	225	NR	1.45 (0.47, 2.33)¶	NR, <0.001
Rivastigmine		Dem	ADAS-Cog 11 (D)	IG1	6	NA	199	53 (26.6)††	NR	NA	225	40 (17.8)††	NR	NR, <0.05
Rivastigmine		Dem	ADAS-Cog 11 (0-70)	IG2	3	NR	226	NR	0.13 (NR)	NR	226	NR	-0.08 (NR)	NS
Rivastigmine		Dem	ADAS-Cog 11 (0-70)	IG2	4	NR	219	NR	0.60 (NR)	NR	218	NR	1.21 (NR)	NS
Rivastigmine		Dem	ADAS-Cog 11 (0-70)	IG2	6	NR	226	NR	1.24 (0.37, 2.23)¶	NR	225	NR	1.45 (0.47, 2.33)¶	NS
Rivastigmine	Rosler, 1999[218] Fair-Good	Dem	ADAS-Cog 11 (D)	IG2	6	NA	226	36 (15.9)††	NR	NA	225	40 (17.8)††	NR	NS
Rivastigmine		Dem	MMSE (0-30)	IG1	6	NR	199	NR	0.34 (-0.25, 0.85)	NR	225	NR	-0.54 (-0.99, -0.01)¶	NR, <0.05
Rivastigmine		Dem	MMSE (0-30)	IG2	6	NR	225	NR	-0.60 (-1.08, -0.12)¶	NR	223	NR	-0.54 (-0.99, -0.01)¶	NR, NR
Rivastigmine	Winblad, 2007[219] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	6	27.9 (9.4)	253	NR	-0.6 (6.2)	28.6 (9.9)	281	NR	1.0 (6.8)	NR, 0.003
Rivastigmine		Dem	ADAS-Cog 11 (0-70)	IG2	6	27.4 (9.7)	262	NR	-1.6 (6.5)	28.6 (9.9)	281	NR	1.0 (6.8)	NR, <0.001
Rivastigmine		Dem	ADAS-Cog 11 (0-70)	IG3	6	27.0 (10.3)	248	NR	-0.6 (6.4)	28.6 (9.9)	281	NR	1.0 (6.8)	NR, 0.005

Appendix E Table 1. AChEIs and Memantine: Detailed Results for Global Cognitive Function Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Rivastigmine		Dem	MMSE (0-30)	IG1	6	16.4 (3.0)	256	NR	0.8 (3.2)	16.4 (3.0)	281	NR	0.0 (3.5)	NR, 0.002
Rivastigmine		Dem	MMSE (0-30)	IG2	6	16.6 (2.9)	262	NR	0.9 (3.4)	16.4 (3.0)	281	NR	0.0 (3.5)	NR, <0.001
Rivastigmine		Dem	MMSE (0-30)	IG3	6	16.7 (3.0)	250	NR	1.1 (3.3)	16.4 (3.0)	281	NR	0.0 (3.5)	NR, 0.002
Memantine	Bakchine, 2008[220] Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	25.9 (10.4)	268	NR	-2.46 (NR)	24.9 (9.7)	135	NR	-0.70 (NR)	MDC (95% CI)=-1.76 (-2.69, -0.83), 0.000
Memantine		Dem	ADAS-Cog 11 (0-70)	IG1	4	25.9 (10.4)	266	NR	-2.26 (NR)	24.9 (9.7)	135	NR	-0.98 (NR)	MDC (95% CI)=-1.29 (-2.33, -0.25), 0.016
Memantine		Dem	ADAS-Cog 11 (0-70)	IG1	6	25.9 (10.4)	268	NR	-1.93 (NR)	24.9 (9.7)	135	NR	-1.08 (NR)	MDC (95% CI)=-0.85 (-2.02, 0.32), 0.156
Memantine	Choi, 2011*[221] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	4	29.1 (8.6)	84	NR	-0.7 (6.6)	27.7 (9.8)	74	NR	-0.04 (7.1)	NR, 0.83
Memantine		Dem	MMSE (0-30)	IG1	4	16.9 (4.3)	84	NR	-0.3 (2.9)	16.7 (4.7)	74	NR	0.1 (2.8)	NR, 0.49
Memantine	Dysken, 2014*[222] Good	Dem	ADAS-Cog 11 (0-70)	IG1	6	19.5 (7.9)	131	NR	1.06‖ (-0.10, 2.32)¶	19.1 (8.1)	128	NR	3.04‖ (1.81, 4.28)¶	NR
Memantine		Dem	ADAS-Cog 11 (0-70)	IG1	12	19.5 (7.9)	116	NR	3.27‖ (1.91, 4.72)¶	19.1 (8.1)	106	NR	4.24‖ (2.81, 5.70)¶	NR
Memantine		Dem	ADAS-Cog 11 (0-70)	IG1	18	19.5 (7.9)	84	NR	5.63‖ (3.90, 7.48)¶	19.1 (8.1)	88	NR	6.04‖ (4.25, 7.86)¶	NR
Memantine	Dysken, 2014*[222] Good	Dem	ADAS-Cog 11 (0-70)	IG1	24	19.5 (7.9)	76	NR	6.69‖ (4.53, 8.91)¶	19.1 (8.1)	69	NR	6.70‖ (4.43, 8.97)¶	NR
Memantine		Dem	ADAS-Cog 11 (0-70)	IG1	30	19.5 (7.9)	51	NR	7.61‖ (5.00, 10.28)¶	19.1 (8.1)	48	NR	8.91‖ (6.20, 11.62)¶	NR
Memantine		Dem	ADAS-Cog 11 (0-70)	IG1	36	19.5 (7.9)	36	NR	8.29‖ (5.20, 11.45)¶	19.1 (8.1)	35	NR	10.76‖ (7.58, 13.96)¶	NR
Memantine		Dem	ADAS-Cog 11 (0-70)	IG1	42	19.5 (7.9)	27	NR	8.21‖ (5.02, 11.46)¶	19.1 (8.1)	25	NR	10.60‖ (7.30, 13.92)¶	NR
Memantine		Dem	ADAS-Cog 11 (0-70)	IG1	48	19.5 (7.9)	142	NR	6.38‖ (0.70)§	19.1 (8.1)	140	NR	7.78‖ (0.70)§	MDC (95% CI)=-1.39 (-2.85, 0.07), 0.25

Appendix E Table 1. AChEIs and Memantine: Detailed Results for Global Cognitive Function Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Memantine		Dem	MMSE (0-30)	IG1	6	20.8 (3.8)	131	NR	-0.25‖ (-0.79, 0.31)¶	20.8 (3.8)	128	NR	-0.33‖ (-0.90, 0.22)¶	NR
Memantine		Dem	MMSE (0-30)	IG1	12	20.8 (3.8)	115	NR	-1.10‖ (-1.76, -0.42)¶	20.8 (3.8)	106	NR	-1.39‖ (-2.08, -0.69)¶	NR
Memantine		Dem	MMSE (0-30)	IG1	18	20.8 (3.8)	85	NR	-2.64‖ (-3.50, -1.73)¶	20.8 (3.8)	88	NR	-2.21‖ (-3.09, -1.31)¶	NR
Memantine		Dem	MMSE (0-30)	IG1	24	20.8 (3.8)	75	NR	-3.46‖ (-4.50, -2.38)¶	20.8 (3.8)	70	NR	-2.90‖ (-3.99, -1.80)¶	NR
Memantine		Dem	MMSE (0-30)	IG1	30	20.8 (3.8)	52	NR	-3.80‖ (-5.01, -2.56)¶	20.8 (3.8)	47	NR	-3.27‖ (-4.53, -2.00)¶	NR
Memantine		Dem	MMSE (0-30)	IG1	36	20.8 (3.8)	36	NR	-4.27‖ (-5.79, -2.72)¶	20.8 (3.8)	36	NR	-3.88‖ (-5.42, -2.31)¶	NR
Memantine		Dem	MMSE (0-30)	IG1	42	20.8 (3.8)	27	NR	-4.62‖ (-6.17, -3.01)¶	20.8 (3.8)	26	NR	-4.68‖ (-6.29, -3.05)¶	NR
Memantine		Dem	MMSE (0-30)	IG1	48	20.8 (3.8)	140	NR	-3.05‖ (0.33)§	20.8 (3.8)	137	NR	-3.16‖ (0.33)§	MDC (95% CI)=0.12 (-0.61, 0.84), 0.84
Memantine	Herrmann, 2013*[224] Fair	Dem	SIB (0-133)	IG1	6	82.25 (1.16)§	159	NR	-2.34 (0.76)§	81.98 (1.00)§	165	NR	-1.86 (0.75)§	MDC (95% CI)=-0.48 (-2.30, 1.34), 0.60
Memantine	Orgogozo, 2002[225] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	20.6 (9.55)	147	NR	0.48 (0.49)	21.5 (8.71)	141	NR	-0.34 (0.30)	NR
Memantine		Dem	ADAS-Cog 11 (0-70)	IG1	6	20.6 (9.55)	147	NR	-0.4 (NR)	21.5 (8.71)	141	NR	1.6 (NR)	MDC (95% CI)=-2.0 (-3.60, -0.49), 0.0016
Memantine		Dem	MMSE (0-30)	IG1	6	NR	105	NR	1.75 (3.38)	NR	108	NR	0.52 (4.07)	NR, 0.0121
Memantine	Peskind, 2006[226] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	27.2 (11.01)	177	NR	-1.20‖ (0.48)§	27.3 (9.74)	177	NR	-0.10‖ (0.48)§	NR, <0.05
Memantine		Dem	ADAS-Cog 11 (0-70)	IG1	4	27.2 (11.01)	163	NR	-1.10‖ (0.56)§	27.3 (9.74)	172	NR	0.40‖ (0.56)§	NR, <0.05
Memantine		Dem	ADAS-Cog 11 (0-70)	IG1	6	27.2 (11.01)	196	NR	-0.93‖ (5.46)	27.3 (9.74)	198	NR	0.44‖ (5.49)	LSM Change (95% CI)=-1.37 (-2.3, -0.48), 0.003

Appendix E Table 1. AChEIs and Memantine: Detailed Results for Global Cognitive Function Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Memantine	Peters, 2015*[227] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	4	20.2 (7.0)§	91	NR	-1.12 (0.57)	18.9 (6.6)§	93	NR	-0.29 (0.57)	NS
Memantine		Dem	ADAS-Cog 11 (0-70)	IG1	6	20.2 (7.0)§	90	NR	-0.29 (0.72)	18.9 (6.6)§	85	NR	0.11 (0.71)	NS
Memantine		Dem	ADAS-Cog 11 (0-70)	IG1	12	20.2 (7.0)§	94	NR	2.00 (0.86)	18.9 (6.6)§	96	NR	1.74 (0.85)	NR, 0.831
Memantine	Porsteinsson, 2008[228] Good	Dem	ADAS-Cog 11 (0-70)	IG1	6	27.9 (10.98)	214	28.5 (12.83)	NR	26.8 (9.88)	213	28.0 (11.94)	NR	MDC (95% CI)=-0.7 (-1.8, 0.1), 0.184
Memantine		Dem	MMSE (0-30)	IG1	6	16.7 (3.68)	210	16.5 (5.38)	NR	17.0 (3.63)	198	16.4 (5.08)	NR	MDC (95% CI)=0.5 (-0.1, 1.1), 0.123
Memantine	Wilcock, 2002[230] Fair-Good	Dem	ADAS-Cog 11 (0-70)	IG1	6	NR	266	NR	-0.53 (7.02)	NR	261	NR	-2.28 (7.77)	MDC (95% CI)=-1.75 (-3.023, -0.49), 0.0005
Memantine	Wilkinson, 2012[231] Fair	Dem	MMSE (0-30)	IG1	12	16.7 (2.4)	103	NR	-0.43 (0.49)§	17.1 (2.4)	114	NR	-0.74 (0.48)§	MDC (SE) : 0.24 (0.46), NS

* New study
† Higher scores indicate better outcomes for all instruments except for ADAS-Cog 11 and ADAS-Cog 13 where lower scores indicate better outcomes
‡ Least squares mean
§ Standard error
‖ Least squares mean change
¶ 95% confidence interval
# Range
** N (%) of participants improving by ≥0 points
†† N (%) of participants improving by ≥4 points
‡‡ N (%) of participants improving by ≥7 points

Abbreviations: AD = Alzheimer's disease; ADAS-Cog 11 = Alzheimer's Disease Assessment Scale-cognitive subscale; 11-item; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-cognitive subscale; 13-item; Adj MD = adjusted mean difference; BL = baseline; CG = control group; CI = confidence interval; D = results are dichotomized; Dem = dementia; FU = followup; IG = intervention group; Int arm = intervention arm; LSM = least squares mean; MCI = mild cognitive impairment; MDC = mean difference in change; MDRS = Mattis Dementia Rating Scale; MMSE = Mini-Mental State Examination; mo. = months; PD = proportion difference; Pop cat = population category; NR = not reported; NS = Not statistically significant; SD = standard deviation; VaD = vascular dementia

Appendix E Table 2. AChEIs and Memantine: Detailed Results for Global Function Dichotomous Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Outcome	Instrument*	Int arm	Time, mo.	IG n at FU	IG FU n (%)	CG n at FU	CG FU n (%)	Between group difference, p-value
Donepezil	Black, 2003[184] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	6	195	140 (71.8)	194	134 (69.1)	NR
Donepezil		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG2	6	196	152 (77.6)	194	134 (69.1)	NR
Donepezil	Burns, 1999[185] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	6	273	172 (63.0)	274	134 (48.9)	NR
Donepezil		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG2	6	211	154 (73.0)	274	134 (48.9)	NR
Donepezil	Feldman, 2001[187] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	6	140	88 (62.8)	146	61 (41.8)	NR, <0.0001
Donepezil	Mohs, 2001[192] Fair	Dem	Number (%) of participants without clinically evident functional decline (CDR/ADL/IADL)	CDR/ADL/IADL (0-365)	IG1	12	207	123 (59.4)	208	92 (44.2)	NR
Donepezil	Mori, 2012[193] Fair	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	3	28	27 (96.4)	30	15 (50.0)	NR
Donepezil		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG2	3	31	26 (83.9)	30	15 (50.0)	NR
Donepezil		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG3	3	32	30 (93.8)	30	15 (50.0)	NR
Donepezil	Rogers, 1996[196] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	3	38	34 (89.5)	40	32 (80.0)	NR

Appendix E Table 2. AChEIs and Memantine: Detailed Results for Global Function Dichotomous Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Outcome	Instrument*	Int arm	Time, mo.	IG n at FU	IG FU n (%)	CG n at FU	CG FU n (%)	Between group difference, p-value
Donepezil		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG2	3	40	33 (82.5)	40	32 (80.0)	NR
Donepezil		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG3	3	41	34 (82.9)	40	32 (80.0)	NR
Donepezil	Rogers, 1998[195] Fair-Good	Dem	Number (%) of participants demonstrating minimal, moderate, or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-7)	IG1	3	152	58 (38.2)	150	27 (18.0)	NR
Donepezil		Dem	Number (%) of participants demonstrating minimal, moderate, or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-7)	IG2	3	153	49 (32.0)	150	27 (18.0)	NR
Donepezil	Salloway, 2004[197] Fair-Good	MCI	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CGIC-MCI (1-7)	IG1	6	89	75 (84.3)	110	93 (84.5)	NS
Donepezil	Wilkinson, 2003[200] Fair-Good	Dem	Number (%) of participants demonstrating minimal, moderate, or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-7)	IG1	6	202	65 (32.2)	188	47 (25.0)	NR, 0.047
Donepezil		Dem	Number (%) of participants demonstrating minimal, moderate, or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-7)	IG2	6	202	79 (39.1)	188	47 (25.0)	NR, 0.004
Donepezil	Winblad, 2001[201] Fair-Good	Dem	Number (%) of participants improved from baseline (GBS)	GBS (0-162)	IG1	3	129	52 (40.3)	129	40 (31.0)	NR
Donepezil		Dem	Number (%) of participants improved from baseline (GBS)	GBS (0-162)	IG1	6	122	47 (38.5)	121	39 (32.2)	NR
Donepezil		Dem	Number (%) of participants improved from baseline (GBS)	GBS (0-162)	IG1	12	93	29 (31.2)	97	21 (21.6)	NR
Donepezil		Dem	Number (%) of participants improved from baseline (GDS)	GDS (1-7)	IG1	3	128	13 (10.2)	130	8 (6.2)	NR
Donepezil	Winblad, 2001[201] Fair-Good	Dem	Number (%) of participants improved from baseline (GDS)	GDS (1-7)	IG1	6	122	14 (11.5)	121	8 (6.6)	NR
Donepezil		Dem	Number (%) of participants improved from baseline (GDS)	GDS (1-7)	IG1	8	105	15 (14.3)	105	7 (6.7)	NR

Appendix E Table 2. AChEIs and Memantine: Detailed Results for Global Function Dichotomous Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Outcome	Instrument*	Int arm	Time, mo.	IG n at FU	IG FU n (%)	CG n at FU	CG FU n (%)	Between group difference, p-value
Donepezil		Dem	Number (%) of participants improved from baseline (GDS)	GDS (1-7)	IG1	12	93	13 (14.0)	98	5 (5.1)	NR, 0.047
Galantamine	Auchus, 2007[202] Fair	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	6	363	274 (75.5)	371	273 (73.6)	NR
Galantamine	Brodaty, 2005[203] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	6	240	191 (79.6)	259	173 (66.8)	NR
Galantamine		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG2	6	246	180 (73.2)	259	173 (66.8)	NR
Galantamine	Erkinjuntti, 2002[204] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	6	288	213 (74.0)	161	95 (59.0)	PD=0.15, 0.001
Galantamine	Raskind, 2000[206] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	6	186	136 (73.1)	196	111 (56.6)	NR
Galantamine		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG2	6	171	118 (69.0)	196	111 (56.6)	NR
Galantamine	Rockwood, 2001[208] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	3	240	194 (80.8)	123	77 (62.6)	NR
Galantamine	Tariot, 2000[209] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	5	253	162 (64.0)	261	128 (49.0)	NR, <0.001
Galantamine	Tariot, 2000[209] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG2	5	256	169 (66.0)	261	128 (49.0)	NR, <0.001

Appendix E Table 2. AChEIs and Memantine: Detailed Results for Global Function Dichotomous Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Outcome	Instrument*	Int arm	Time, mo.	IG n at FU	IG FU n (%)	CG n at FU	CG FU n (%)	Between group difference, p-value
Galantamine		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG3	5	128	68 (53.1)	261	128 (49.0)	NR
Galantamine	Wilcock, 2000[210] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	6	206	127 (61.7)	203	101 (49.8)	NR, <0.05
Galantamine		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG2	6	198	130 (65.7)	203	101 (49.8)	NR, <0.001
Galantamine	Wilkinson, 2001[211] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-5)	IG1	3	53	44 (83.0)	83	57 (68.7)	NR
Galantamine		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-5)	IG2	3	47	41 (87.2)	83	57 (68.7)	NR
Galantamine		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-5)	IG3	3	79	67 (84.8)	83	57 (68.7)	NR
Rivastigmine	Agid, 1998[212] Fair-Good	Dem	Number (%) of participants demonstrating moderate or marked improvement (CIBIC+ score ≤2)	CIBIC+ (1-7)	IG1	3	103	44 (42.7)	117	35 (29.9)	NR, 0.05
Rivastigmine		Dem	Number (%) of participants demonstrating moderate or marked improvement (CIBIC+ score ≤2)	CIBIC+ (1-7)	IG2	3	111	35 (31.5)	117	35 (29.9)	NS
Rivastigmine	Corey-Bloom, 1998[214] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	6	145	35 (24.1)	192	31 (16.1)	NR
Rivastigmine		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG2	6	194	49 (25.3)	192	31 (16.1)	NR

Appendix E Table 2. AChEIs and Memantine: Detailed Results for Global Function Dichotomous Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Outcome	Instrument*	Int arm	Time, mo.	IG n at FU	IG FU n (%)	CG n at FU	CG FU n (%)	Between group difference, p-value
Rivastigmine	Feldman, 2007[215] Fair	Dem	Number (%) of participants demonstrating minimal, moderate, or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-7)	IG1	3	220	66 (30.0)	213	34 (16.0)	NR, 0.001
Rivastigmine		Dem	Number (%) of participants demonstrating minimal, moderate, or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-7)	IG1	4	220	67 (30.5)	213	40 (18.8)	NR, 0.001
Rivastigmine		Dem	Number (%) of participants demonstrating minimal, moderate, or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-7)	IG1	6	220	67 (30.5)	213	40 (18.8)	NR, <0.05
Rivastigmine		Dem	Number (%) of participants demonstrating minimal, moderate, or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-7)	IG2	3	215	62 (28.8)	213	34 (16.0)	NR, <0.05
Rivastigmine		Dem	Number (%) of participants demonstrating minimal, moderate, or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-7)	IG2	4	215	47 (21.9)	213	40 (18.8)	NS
Rivastigmine		Dem	Number (%) of participants demonstrating minimal, moderate, or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-7)	IG2	6	215	49 (22.8)	213	40 (18.8)	NS
Rivastigmine	Rosler, 1999[218] Fair-Good	Dem	Number (%) of participants demonstrating minimal, moderate, or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-7)	IG1	6	193	78 (40.4)	220	44 (20.0)	NR, <0.001
Rivastigmine		Dem	Number (%) of participants demonstrating minimal, moderate, or marked improvement (CIBIC+ score ≤3)	CIBIC+ (1-7)	IG2	6	224	71 (31.7)	220	44 (20.0)	NR, <0.01
Rivastigmine	Winblad, 2007[219] Fair	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	6	253	188 (74.3)	278	169 (60.8)	NR
Rivastigmine		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG2	6	260	179 (68.8)	278	169 (60.8)	NR

Appendix E Table 2. AChEIs and Memantine: Detailed Results for Global Function Dichotomous Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Outcome	Instrument*	Int arm	Time, mo.	IG n at FU	IG FU n (%)	CG n at FU	CG FU n (%)	Between group difference, p-value
Rivastigmine	Winblad, 2007[219] Fair	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG3	6	248	182 (73.4)	278	169 (60.8)	NR
Memantine	Orgogozo, 2002[225] Fair-Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CGIC (1-7)	IG1	6	93	74 (79.6)	94	66 (70.2)	NR, 0.227
Memantine		Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	6	147	88 (59.9)	141	74 (52.5)	NR
Memantine	Saxton, 2012[229] Good	Dem	Number (%) of participants demonstrating no change or marked improvement (CIBIC+ score ≤4)	CIBIC+ (1-7)	IG1	3	133	97 (72.9)	124	78 (62.9)	NR

* Lower scores indicate better outcomes for all instruments

Abbreviations: CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; CG = control group; CGI = Clinical Global Impression scale; CIBIC+ = Clinician's Interview-Based Impression of Change with caregiver's input; Dem = dementia; FU = followup; GBS = Gottfries-Brane-Steen scale; GDS = Global Deterioration Scale; IG = intervention group; Int arm = intervention arm; MCI = mild cognitive impairment; mo. = months; PD = proportion difference; Pop cat = population category; n = number of participants analyzed; NR = not reported

Appendix E Table 3. AChEIs and Memantine: Detailed Results for Global Function Continuous Outcomes, by Medication Type

Medication	Author, year Quality	Instrument (range)*	Pop cat	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Donepezil	Black, 2003[184] Fair-Good	CIBIC+ (1-7)	Dem	IG1	6	NA	195	3.9 (NR)	NR	NA	194	4.0 (NR)	NR	NR
Donepezil		CIBIC+ (1-7)	Dem	IG2	6	NA	196	3.8 (NR)	NR	NA	194	4.0 (NR)	NR	NR
Donepezil		CDR-SB (0-18)	Dem	IG1	6	6.1† (0.2)‡	195	NR	-0.25§ (0.11)‡	6.1† (0.2)‡	194	NR	0.11§ (0.12)	NR, <0.05
Donepezil		CDR-SB (0-18)	Dem	IG2	6	6.4† (0.2)‡	196	NR	-0.01§ (0.12)‡	6.1† (0.2)	194	NR	0.11§ (0.12)‡	NS
Donepezil	Burns, 1999[185] Fair-Good	CIBIC+ (1-7)	Dem	IG1	3	NA	202	3.90 (0.06)‡	NR	NA	219	4.23 (0.06)‡	NR	NR, 0.0001
Donepezil		CIBIC+ (1-7)	Dem	IG1	4	NA	202	4.00 (0.07)‡	NR	NA	219	4.45 (0.07)‡	NR	NR, <0.0001
Donepezil		CIBIC+ (1-7)	Dem	IG1	6	NA	273	4.12 (0.07)‡	NR	NA	274	4.51 (0.06)‡	NR	NR, 0.0002
Donepezil		CIBIC+ (1-7)	Dem	IG2	3	NA	211	4.02 (0.07)‡	NR	NA	219	4.23 (0.06)‡	NR	NR, 0.0010
Donepezil		CIBIC+ (1-7)	Dem	IG2	4	NA	211	4.08 (0.06)‡	NR	NA	219	4.45 (0.07)‡	NR	NR, 0.0326
Donepezil		CIBIC+ (1-7)	Dem	IG2	6	NA	271	4.22 (0.08)‡	NR	NA	274	4.51 (0.06)‡	NR	NR, 0.0072
Donepezil		CDR-SB (0-18)	Dem	IG1	3	NR	202	NR	-0.18§ (0.08)‡	NR	219	NR	0.15§ (0.08)‡	NR, 0.0014
Donepezil		CDR-SB (0-18)	Dem	IG1	4	NR	202	NR	-0.17§ (0.11)‡	NR	219	NR	0.33§ (0.11)‡	NR, 0.0006
Donepezil		CDR-SB (0-18)	Dem	IG1	6	NR	273	NR	-0.06§ (0.10)‡	NR	274	NR	0.36§ (0.10)‡	-0.4, 0.0033
Donepezil		CDR-SB (0-18)	Dem	IG2	3	NR	211	NR	-0.17§ (0.08)‡	NR	219	NR	0.15§ (0.08)‡	NR, 0.0021
Donepezil		CDR-SB (0-18)	Dem	IG2	4	NR	211	NR	-0.02§ (0.10)‡	NR	219	NR	0.32§ (0.11)‡	NR, 0.0154
Donepezil		CDR-SB (0-18)	Dem	IG2	6	NR	271	NR	0.06§ (0.10)‡	NR	274	NR	0.36§ (0.10)‡	0.3, 0.0344
Donepezil	Doody, 2009[186] Fair	CIBIC+ (1-7)	MCI	IG1	11	NA	379	3.9 (0.1)‡	NR	NA	378	3.9 (0.1)‡	NR	NS
Donepezil		CDR-SB (0-18)	MCI	IG1	11	1.5 (0.9)	379	NR	0.0 (0.1)‡	1.5 (0.9)	378	NR	0.1 (0.1)	NS
Donepezil	Feldman, 2001[187] Fair-Good	CIBIC+ (1-7)	Dem	IG1	3	NA	127	3.58† (0.08)‡	NR	NA	132	4.06† (0.08)‡	NR	NR, <0.0001
Donepezil		CIBIC+ (1-7)	Dem	IG1	4	NA	122	3.72† (0.09)‡	NR	NA	126	4.26† (0.10)‡	NR	NR, <0.0001

Appendix E Table 3. AChEIs and Memantine: Detailed Results for Global Function Continuous Outcomes, by Medication Type

Medication	Author, year Quality	Instrument (range)*	Pop cat	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Donepezil		CIBIC+ (1-7)	Dem	IG1	6	NA	140	4.04[†] (0.09)[‡]	NR	NA	146	4.57[†] (0.09)[‡]	NR	MD=-0.54, <0.0001
Donepezil	Mazza, 2006[191] Fair-Good	CGI Item 2 (1-7)	Dem	IG1	6	4.5 (0.76)	25	NR	-0.9 (-1.2, -0.5)[‖]	5.05 (0.99)	26	NR	0.15 (-0.02, 0.3)[‖]	MDC (95 CI)%=-1.6 (-2.2, -0.9), <0.001
Donepezil	Mohs, 2001[192] Fair	CDR/ADL/IADL (0-365)	Dem	IG1	12	NR	207	357[¶] (NR)	NR	NR	208	208[¶] (NR)	NR	NR
Donepezil	Mori, 2012[193] Fair	CIBIC+ (1-7)	Dem	IG1	3	NA	28	3.1 (NR)	NR	NA	30	4.3 (NR)	NR	NR
Donepezil		CIBIC+ (1-7)	Dem	IG2	3	NA	31	3.0 (NR)	NR	NA	30	4.3 (NR)	NR	NR
Donepezil		CIBIC+ (1-7)	Dem	IG3	3	NA	32	3.2 (NR)	NR	NA	30	4.3 (NR)	NR	NR
Donepezil	Petersen, 2005[194] Fair	CDR-SB (0-18)	MCI	IG1	12	1.80 (0.8)	NR	NR	0.25 (0.92)	1.87 (0.8)	NR	NR	0.40 (1.28)	NR
Donepezil		CDR-SB (0-18)	MCI	IG1	18	1.80 (0.8)	NR	NR	0.51 (1.18)	1.87 (0.8)	NR	NR	0.72 (1.55)	NR
Donepezil		CDR-SB (0-18)	MCI	IG1	24	1.80 (0.8)	NR	NR	0.87 (1.55)	1.87 (0.8)	NR	NR	0.97 (1.76)	NR
Donepezil		CDR-SB (0-18)	MCI	IG1	30	1.80 (0.8)	NR	NR	1.19 (1.69)	1.87 (0.8)	NR	NR	1.26 (2.15)	NR
Donepezil		CDR-SB (0-18)	MCI	IG1	36	1.80 (0.8)	161	NR	1.60 (2.09)	1.87 (0.8)	193	NR	1.64 (2.55)	NR
Donepezil		CDR-SB (0-18)	MCI	IG1	6	1.80 (0.8)	NR	NR	0.05 (0.66)	1.87 (0.8)	NR	NR	0.14 (0.86)	NR
Donepezil		GDS (1-7)	MCI	IG1	12	2.66 (0.6)	NR	NR	0.11 (0.57)	2.72 (0.6)	NR	NR	0.15 (0.65)	NR
Donepezil		GDS (1-7)	MCI	IG1	18	2.66 (0.6)	NR	NR	0.19 (0.66)	2.72 (0.6)	NR	NR	0.27 (0.73)	NR, <0.05
Donepezil		GDS (1-7)	MCI	IG1	24	2.66 (0.6)	NR	NR	0.32 (0.73)	2.72 (0.6)	NR	NR	0.38 (0.81)	NR
Donepezil		GDS (1-7)	MCI	IG1	30	2.66 (0.6)	NR	NR	0.45 (0.78)	2.72 (0.6)	NR	NR	0.48 (0.87)	NR
Donepezil		GDS (1-7)	MCI	IG1	36	2.66 (0.6)	161	NR	0.59 (0.89)	2.72 (0.6)	193	NR	0.56 (0.99)	NR
Donepezil		GDS (1-7)	MCI	IG1	6	2.66 (0.6)	NR	NR	-0.01 (0.52)	2.72 (0.6)	NR	NR	0.07 (0.53)	NR
Donepezil	Rogers, 1996[196] Fair-Good	CDR-SB (0-18)	Dem	IG1	3	7.3 (NR)	38	NR	0.11 (-2.0, 3.0)[#]	6.7 (NR)	40	NR	0.10 (-2.0, 3.0)[#]	NS
Donepezil		CDR-SB (0-18)	Dem	IG2	3	6.9 (NR)	40	NR	0.23 (-3.0, 6.0)[#]	6.7 (NR)	40	NR	0.10 (-2.0, 3.0)[#]	NS
Donepezil		CDR-SB (0-18)	Dem	IG3	3	6.6 (NR)	41	NR	0.18 (-2.0, 5.0)[#]	6.7 (NR)	40	NR	0.10 (-2.0, 3.0)[#]	NS
Donepezil	Rogers, 1998[195] Fair-Good	CIBIC+ (1-7)	Dem	IG1	3	NA	152	Mean (SE): 3.8 (0.08)[‡]	NR	NA	150	Mean (SE): 4.2 (0.07)	NR	MD (95% CI)=-0.4 (-0.55, -0.13), 0.008
Donepezil	Rogers, 1998[195] Fair-Good	CIBIC+ (1-7)	Dem	IG2	3	NA	153	3.9 (0.08)[‡]	NR	NA	150	4.2 (0.07)[‡]	NR	MD (95% CI)=-0.3 (-0.50, -0.08), 0.003

Appendix E Table 3. AChEIs and Memantine: Detailed Results for Global Function Continuous Outcomes, by Medication Type

Medication	Author, year Quality	Instrument (range)*	Pop cat	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Donepezil		CDR-SB (0-18)	Dem	IG1	3	7.18 (0.20)‡	154	NR	-0.31§ (0.11)‡	6.81 (0.18)‡	150	NR	-0.14§ (0.11)‡	MDC (95% CI)=NR (-0.46, 0.12), NS
Donepezil		CDR-SB (0-18)	Dem	IG2	3	6.85 (0.18)‡	156	NR	-0.10§ (0.11)‡	6.81 (0.18)‡	150	NR	0.14§ (0.11)‡	MDC (95% CI)=NR (-0.25, 0.33), 0.32
Donepezil	Wilkinson, 2003[200] Fair-Good	CIBIC+ (1-7)	Dem	IG1	6	NA	202	3.9 (NR)	NR	NA	188	4.1 (NR)	NR	NR, 0.047
Donepezil		CIBIC+ (1-7)	Dem	IG2	6	NA	202	3.7 (NR)	NR	NA	188	4.1 (NR)	NR	NR, 0.004
Donepezil		CDR-SB (0-18)	Dem	IG1	6	6.1 (0.2)‡	203	NR	-0.21§ (0.12)‡	5.6 (0.2)‡	188	NR	0.16§ (0.13)‡	NR, 0.03
Donepezil		CDR-SB (0-18)	Dem	IG2	6	6.0† (0.2)‡	202	NR	-0.15§ (0.12)‡	5.6† (0.2)	188	NR	0.16§ (0.13)‡	NR, 0.07
Donepezil	Winblad, 2001[201] Fair-Good	GBS (0-162)	Dem	IG1	12	29.51 (17.33)	138	NR	8.05§ (1.53)‡	29.77 (17.84)	144	NR	11.47§ (1.48)‡	NR, 0.054
Donepezil		GBS (0-162)	Dem	IG1	3	29.51 (17.33)	129	NR	1.56§ (1.35)‡	29.77 (17.84)	129	NR	2.78§ (1.03)‡	NS
Donepezil		GBS (0-162)	Dem	IG1	6	29.51 (17.33)	122	NR	1.78§ (1.30)‡	29.77 (17.84)	121	NR	4.93§ (1.38)‡	NR, 0.046
Donepezil		GBS (0-162)	Dem	IG1	8	29.51 (17.33)	105	NR	3.87§ (1.86)‡ (2.01, 5.43)‖	29.77 (17.84)	105	NR	9.14§ (1.88)‡ (7.26, 10.99)‖	NR, 0.012
Donepezil		GDS (1-7)	Dem	IG1	12	4.15 (0.83)	136	NR	0.25§ (0.07)‡	4.16 (0.90)	140	NR	0.44§ (0.06)‡	NR, 0.014
Donepezil		GDS (1-7)	Dem	IG1	3	4.15 (0.83)	128	NR	-0.33 (NR)	4.16 (0.90)	130	NR	-0.30 (NR)	NR, 0.26
Donepezil		GDS (1-7)	Dem	IG1	6	4.15 (0.83)	122	NR	0.01§ (0.07)‡	4.16 (0.90)	121	NR	0.17§ (0.17)‡	NR, 0.004
Donepezil		GDS (1-7)	Dem	IG1	8	4.15 (0.83)	105	NR	0.09§ (0.07)‡	4.16 (0.90)	105	NR	0.37§ (0.08)‡	NR, 0.011
Galantamine	Brodaty, 2005[203] Fair-Good	CIBIC+ (1-7)	Dem	IG1	6	NA	240	5.3 (NR)	NR	NA	259	5.1 (NR)	NR	NR
Galantamine		CIBIC+ (1-7)	Dem	IG2	6	NA	246	5.3 (NR)	NR	NA	259	5.1 (NR)	NR	NR
Galantamine	Raskind, 2000[206] Fair-Good	CIBIC+ (1-7)	Dem	IG1	6	NA	186	5.3 (NR)	NR	NA	259	5.1 (NR)	NR	NR
Galantamine		CIBIC+ (1-7)	Dem	IG2	6	NA	171	5.3 (NR)	NR	NA	259	5.1 (NR)	NR	NR

Appendix E Table 3. AChEIs and Memantine: Detailed Results for Global Function Continuous Outcomes, by Medication Type

Medication	Author, year Quality	Instrument (range)*	Pop cat	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Galantamine	Rockwood, 2001[206] Fair-Good	CIBIC+ (1-7)	Dem	IG1	3	NA	240	5.3 (NR)	NR	NA	259	5.1 (NR)	NR	NR
Galantamine	Rockwood, 2006[207] Fair	CIBIC+ (1-7)	Dem	IG1	4	NA	61	5.3 (NR)	NR	NA	259	5.1 (NR)	NR	0.03
Galantamine	Wilcock, 2000[210]	CIBIC+ (1-7)	Dem	IG1	6	NA	206	5.3 (NR)	NR	NA	259	5.1 (NR)	NR	NR, <0.05
Galantamine	Fair-Good	CIBIC+ (1-7)	Dem	IG2	6	NA	198	5.3 (NR)	NR	NA	259	5.1 (NR)	NR	NR, <0.001
Rivastigmine	Ballard, 2008[213] Fair	CIBIC+ (1-7)	Dem	IG1	6	NA	329	4.0 (1.31)	NR	NA	320	4.1 (1.27)	NR	MD=0.1, NS
Rivastigmine		GDS (1-7)	Dem	IG1	6	4.0 (0.8)	365	NR	-0.1 (0.85)	4.0 (0.8)	345	NR	0.0 (0.69)	MDC=0.1, NS
Rivastigmine	Corey-Bloom, 1998[214] Fair-Good	GDS (1-7)	Dem	IG1	6	4.0 (NR)	231	NR	-0.13 (-0.22, -0.04)[ll]	3.9 (NR)	234	NR	-0.32 (-0.41, -0.23)[ll]	MDC (95% CI): 0.19 (0.06, 0.32), <0.030
Rivastigmine		GDS (1-7)	Dem	IG2	6	4.0 (NR)	233	NR	-0.16 (-0.25, -0.07)[ll]	3.9 (NR)	234	NR	-0.32 (-0.41, -0.23)[ll]	NR
Rivastigmine	Feldman, 2007[215] Fair	CIBIC+ (1-7)	Dem	IG1	6	NA	222	3.9 (1.3)	NR	NR	216	4.5 (1.3)	NR	Cohen's d=0.46, NR
Rivastigmine		CIBIC+ (1-7)	Dem	IG2	6	NA	222	4.1 (1.3)	NR	NR	216	4.5 (1.3)	NR	Cohen's d=0.31,
Rivastigmine		GDS (1-7)	Dem	IG1	6	4.1 (0.9)	227	NR	0.0 (0.7)	4.1 (0.9)	222	NR	-0.3 (0.7)	NR
Rivastigmine		GDS (1-7)	Dem	IG2	6	4.0 (0.9)	227	NR	-0.2 (0.7)	4.1 (0.9)	222	NR	-0.3 (0.7)	NR
Rivastigmine	Mok, 2007[217] Fair	CDR-SB (0-18)	Dem	IG1	6	8.7 (5.1)	20	9.4 (5.5)	NR	9.1 (4.6)	19	9.5 (5.4)	NR	NR, 0.787
Rivastigmine	Rosler, 1999[218] Fair-Good	CIBIC+ (1-7)	Dem	IG1	3	NA	191	3.88 (NR)	NR	NA	226	3.96 (NR)	NR	NR, <0.05
Rivastigmine		CIBIC+ (1-7)	Dem	IG1	4	NA	179	3.85 (NR)	NR	NA	218	4.09 (NR)	NR	NR, <0.05
Rivastigmine		CIBIC+ (1-7)	Dem	IG1	6	NA	193	3.88 (NR)	NR	NA	220	4.32 (NR)	NR	NR, <0.001
Rivastigmine		CIBIC+ (1-7)	Dem	IG2	6	NA	224	4.17 (NR)	NR	NA	220	4.32 (NR)	NR	NR, >0.05
Rivastigmine	Rosler, 1999[218] Fair-Good	GDS (1-7)	Dem	IG1	6	NR	198	NR	-0.03 (-0.13, 0.13)[ll]	NR	223	NR	-0.24 (-0.31, -0.09)[ll]	NR, <0.05

Appendix E Table 3. AChEIs and Memantine: Detailed Results for Global Function Continuous Outcomes, by Medication Type

Medication	Author, year Quality	Instrument (range)*	Pop cat	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Rivastigmine		GDS (1-7)	Dem	IG2	6	NR	225	NR	-0.20 (-0.31, -0.09)‖	NR	223	NR	-0.24 (-0.31, -0.09)‖	NR
Rivastigmine	Winblad, 2007[219] Fair	CIBIC+ (1-7)	Dem	IG1	6	NA	253	3.9 (1.3)	NR	NA	278	4.2 (1.3)	NR	NR, 0.009
Rivastigmine		CIBIC+ (1-7)	Dem	IG2	6	NA	260	4.0 (1.3)	NR	NA	278	4.2 (1.3)	NR	NR, 0.054
Rivastigmine		CIBIC+ (1-7)	Dem	IG3	6	NA	248	3.9 (1.2)	NR	NA	278	4.2 (1.3)	NR	NR, 0.01
Memantine	Bakchine, 2008[220] Good	CIBIC+ (1-7)	Dem	IG1	3	NA	267	5.3 (NR)	NR	NA	259	5.1 (NR)	NR	MD (95% CI)=-0.21 (-0.40, -0.02), 0.033
Memantine		CIBIC+ (1-7)	Dem	IG1	4	NA	268	5.3 (NR)	NR	NA	259	5.1 (NR)	NR	MD (95% CI)=-0.28 (-0.49, -0.06), 0.012
Memantine		CIBIC+ (1-7)	Dem	IG1	6	NA	268	5.3 (NR)	NR	NA	259	5.1 (NR)	NR	MD (95% CI)=-0.07 (-0.30, 0.15), 0.523
Memantine	Choi, 2011**[221] Fair	CDR-SB (0-18)	Dem	IG1	4	5.92 (3.08)	84	NR	0.45 (1.72)	5.84 (3.51)	74	NR	0.34 (1.55)	NR, 0.71
Memantine	Orgogozo, 2002[225] Fair-Good	CGIC (1-7)	Dem	IG1	6	NA	116	3.58 (1.09)	NR	NA	117	3.85 (1.19)	NR	NR, 0.0938
Memantine		CIBIC+ (1-7)	Dem	IG1	6	NA	114	3.82 (1.39)	NR	NA	114	4.11 (1.48)	NR	NR, 0.284
Memantine		GBS (0-162)	Dem	IG1	6	NR	114	NR	-0.36 (15.38)	NA	118	NR	3.38 (16.34)	NR, 0.1194
Memantine	Peskind, 2006[226] Fair-Good	CIBIC+ (1-7)	Dem	IG1	3	NA	178	3.99 (0.80)	NR	NA	179	4.18 (0.85)	NR	NR, 0.02
Memantine		CIBIC+ (1-7)	Dem	IG1	4	NA	167	4.17 (0.88)	NR	NA	172	4.43 (0.90)	NR	NR, 0.03
Memantine		CIBIC+ (1-7)	Dem	IG1	6	NA	195	4.20 (0.96)	NR	NA	198	4.52 (1.06)	NR	NR, 0.004
Memantine	Peters, 2015**[227] Fair	CDR-SB (0-18)	Dem	IG1	12	5.0 (1.5)‡	94	NR	1.14 (0.25)	4.8 (1.4)‡	96	NR	1.17 (0.25)	NR, 0.921
Memantine		CDR-SB (0-18)	Dem	IG1	4	5.0 (1.5)‡	94	NR	0.092 (0.17)	4.8 (1.4)‡	94	NR	0.44 (0.26)	NS
Memantine		CDR-SB (0-18)	Dem	IG1	6	5.0 (1.5)‡	87	NR	0.32 (0.15)	4.8 (1.4)‡	90	NR	0.22 (0.14)	NS
Memantine	Peters, 2015**[227] Fair	CDR-SB (0-18)	Dem	IG1	9	5.0 (1.5)‡	86	NR	0.40 (0.20)	4.8 (1.4)‡	91	NR	0.51 (0.19)	NS

Appendix E Table 3. AChEIs and Memantine: Detailed Results for Global Function Continuous Outcomes, by Medication Type

Medication	Author, year Quality	Instrument (range)*	Pop cat	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Memantine	Porsteinsson, 2008[228] Good	CIBIC+ (1-7)	Dem	IG1	6	NA	214	4.38 (1.00)	NR	NA	213	4.42 (0.96)	NR	MD (95% CI)=0.0 (-0.2, 0.2), 0.843

* Lower scores indicate better outcomes for all instruments
† Least squares mean
‡ Standard error
§ Least squares mean change
‖ 95% confidence interval
¶ Median
# Range
** New study

Abbreviations: BL = baseline; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; CG = control group; CGI = Clinical Global Impression scale; CI = confidence interval; CIBIC+ = Clinician's Interview-Based Impression of Change with caregiver's input; Dem = dementia; FU = followup; GBS = Gottfries-Brane-Steen scale; GDS = Global Deterioration Scale; IG = intervention group; Int arm = intervention arm; MCI = mild cognitive impairment; MDC = mean difference in change; mo. = months; Pop cat = population category; NR = not reported; NS = not statistically significant; SD = standard deviation

Appendix E Table 4. AChEIs and Memantine: Detailed Results for Physical Function Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	ADL or ADL, (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SE)	IG n at FU	IG FU mean (SE)	IG mean change (SE or 95% CI) from BL	CG BL mean (SE)	CG n at FU	CG FU mean (SE)	CG mean change (SE or 95% CI) from BL	Between group difference, p-value
Donepezil	Black, 2003[184] Fair-Good	Dem	ADL/IADL (ADFACS, 0-54, ↓)	IG1	6	15.3* (0.7)	180	NR	0.53† (0.38)	15.9* (0.7)	189	NR	1.44† (0.42)	NR
Donepezil		Dem	ADL/IADL (ADFACS, 0-54, ↓)	IG2	6	17.3* (0.8)	181	NR	0.64† (0.36)	15.9* (0.7)	180	NR	1.44† (0.42)	NR
Donepezil		Dem	IADL (ADFACS-IADL, 0-30, ↓)	IG1	6	NR	189	NR	0.13† (0.27)	NR	180	NR	0.87† (0.32)	NR
Donepezil		Dem	IADL (ADFACS-IADL, 0-30, ↓)	IG2	6	NR	181	NR	-0.02† (0.25)	NR	180	NR	0.87† (0.87)	NR, <0.05
Donepezil	Burns, 1999[185] Fair-Good	Dem	ADL/IADL (IDDD - performance scale, 33-231, ↓)	IG1	3	69.85 (1.71)	202	67.94 (0.40)	NR	69.84 (1.68)	219	69.75 (0.74)	NR	NR, 0.0085
Donepezil		Dem	ADL/IADL (IDDD - performance scale, 33-231, ↓)	IG1	4	69.85 (1.71)	202	68.66 (0.40)	NR	69.84 (1.68)	219	70.93 (0.48)	NR	NR, 0.0033
Donepezil		Dem	ADL/IADL (IDDD - performance scale, 33-231, ↓)	IG1	6	69.85 (1.71)	273	69.30 (0.46)	NR	69.84 (1.68)	274	71.45 (1.94)	NR	NR, 0.0072
Donepezil		Dem	ADL/IADL (IDDD - performance scale, 33-231, ↓)	IG2	3	67.78 (1.61)	211	68.94 (0.36)	NR	69.84 (1.68)	219	69.75 (0.74)	NR	NR
Donepezil		Dem	ADL/IADL (IDDD - performance scale, 33-231, ↓)	IG2	4	67.78 (1.61)	211	69.46 (0.40)	NR	69.84 (1.68)	219	70.93 (0.48)	NR	NR
Donepezil		Dem	ADL/IADL (IDDD - performance scale, 33-231, ↓)	IG2	6	67.78 (1.61)	271	70.36 (0.45)	NR	69.84 (1.68)	274	71.45 (1.94)	NR	NR, 0.0072
Donepezil	Feldman, 2001[187] Fair-Good	Dem	ADL/IADL (DAD, 0-100, ↑)	IG1	3	52.11 (2.07)	127	NR	1.51† (1.28)	54.07 (2.00)	132	NR	-3.16† (1.22)	NR, 0.0037
Donepezil		Dem	ADL/IADL (DAD, 0-100, ↑)	IG1	6	52.11 (2.07)	134	NR	-0.74† (1.31)	54.07 (2.00)	140	NR	-8.98† (1.40)	MDC=8.23, <0.0001
Donepezil		Dem	IADL (Lawton and Brody IADL, NR, ↑)	IG1	6	64.34 (2.06)	144	NR	NR	63.88 (1.97)	146	NR	NR	MDC=6.83, <0.0001
Donepezil		Dem	ADL (PSMS, NR, ↑)	IG1	6	7.90 (0.43)	144	NR	NR	7.63 (0.41)	146	NR	NR	MDC=1.32, 0.0015
Donepezil	Petersen, 2005[194] Fair	MCI	IADL (ADCS-MCI-ADL, 0-53, ↑)	IG1	12	46.49 (4.3)‡	NR	NR	-1.41 (4.48)‡	45.87 (5.2)‡	NR	NR	-1.44 (5.00)‡	NR
Donepezil		MCI	IADL (ADCS-MCI-ADL, 0-53, ↑)	IG1	18	46.49 (4.3)‡	NR	NR	1.78 (5.02)‡	45.87 (5.2)‡	NR	NR	-2.34 (6.02)‡	NR
Donepezil		MCI	IADL (ADCS-MCI-ADL, 0-53, ↑)	IG1	24	46.49 (4.3)‡	NR	NR	-3.09 (6.24)‡	45.87 (5.2)‡	NR	NR	-3.43 (6.73)‡	NR

Appendix E Table 4. AChEIs and Memantine: Detailed Results for Physical Function Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	ADL or ADL, (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SE)	IG n at FU	IG FU mean (SE)	IG mean change (SE or 95% CI) from BL	CG BL mean (SE)	CG n at FU	CG FU mean (SE)	CG mean change (SE or 95% CI) from BL	Between group difference, p-value
Donepezil		MCI	IADL (ADCS-MCI-ADL, 0-53, ↑)	IG1	30	46.49 (4.3)‡	NR	-4.44 (7.39)‡	NR	45.87 (5.2)‡	NR	-5.00 (8.05)‡	NR	NR
Donepezil		MCI	IADL (ADCS-MCI-ADL, 0-53, ↑)	IG1	36	46.49 (4.3)‡	161	NR	-6.26 (8.67)‡	45.87 (5.2)‡	193	NR	-6.39 (8.99)‡	NR
Donepezil		MCI	IADL (ADCS-MCI-ADL, 0-53, ↑)	IG1	6	46.49 (4.3)‡	NR	NR	-0.21 (3.43)‡	45.87 (5.2)‡	NR	NR	-1.06 (4.54)‡	NR
Donepezil	Rogers, 1996[196] Fair-Good	Dem	ADL/IADL (Unified ADL, NR, ↓)	IG1	3	105.5 (NR)	38	NR	-3.1 (-36, 15)§	92.4 (NR)	40	NR	1.5 (-38, 57)§	NR, NS
Donepezil		Dem	ADL/IADL (Unified ADL, NR, ↓)	IG2	3	98.8 (NR)	40	NR	0.6 (-21, 30)§	92.4 (NR)	40	NR	1.5 (-38, 57)§	NR, NS
Donepezil		Dem	ADL/IADL (Unified ADL, NR, ↓)	IG3	3	94.7 (NR)	41	NR	4.0 (-25, 97)§	92.4 (NR)	40	NR	1.5 (-38, 57)§	NR, NS
Donepezil	Wilkinson, 2003[200] Fair-Good	Dem	ADL/IADL (ADFACS, 0-54, ↓)	IG1	6	16.1* (0.7)	203	NR	-0.23† (0.40)	15.1* (0.7)	188	NR	0.76† (0.39)	NS
Donepezil		Dem	ADL/IADL (ADFACS, 0-54, ↓)	IG2	6	15.7* (0.7)	202	NR	0.11† (0.45)	15.1* (0.7)	188	NR	0.76† (0.39)	NS
Donepezil	Winblad, 2001[201] Fair-Good	Dem	ADL/IADL (ADFACS, 0-54, ↓)	IG1	12	52.77 (20.58)‡	93	NR	-11.19† (NR)	52.93 (20.45)‡	97	NR	-15.25† (NR)	NR, <0.05
Galantamine	Auchus, 2007[202] Fair	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	48.3 (17.2)‡	388	NR	0.8 (9.78)	45.9 (16.8)‡	379	NR	0.2 (9.12)	NR, 0.789
Galantamine	Brodaty, 2005[203] Fair-Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	3	52.0 (0.90)	279	NR	1.1 (0.47)	54.5 (0.87)	281	NR	-0.3 (0.46)	NR
Galantamine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	52.0 (0.90)	242	NR	-1.0 (0.05)	54.5 (0.87)	258	NR	-2.7 (0.56)	NR (95% CI)=(0.22, 3.04), 0.018
Galantamine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG2	3	53.5 (0.88)	276	NR	0.4 (0.48)	54.5 (0.87)	281	NR	-0.3 (0.46)	NR
Galantamine	Brodaty, 2005[203] Fair-Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG2	6	53.5 (0.88)	245	NR	0.0 (0.48)	54.5 (0.87)	258	NR	-2.7 (0.56)	NR (95% CI)=(1.09, 3.91), <0.001
Galantamine	Erkinjuntti, 2002[204] Fair-Good	Dem	ADL/IADL (DAD, 0-100, ↑)	IG1	6	NR	288	NR	0.2 (0.9)	NR	161	NR	-4.4 (1.3)	MDC=4.6, 0.0017
Galantamine	Hager, 2014[II206] Fair	Dem	ADL/IADL (DAD, 0-100, ↑)	IG1	12	61.8 (21.61)‡	811	NR	-4.55 (14.68)‡	60.9 (21.09)‡	822	NR	-6.50 (16.17)‡	NR, 0.009
Galantamine		Dem	ADL/IADL (DAD, 0-100, ↑)	IG1	24	61.8 (21.61)‡	810	NR	-8.16 (17.25)‡	60.9 (21.09)‡	822	NR	-10.81 (18.27)‡	NR, 0.002

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Medication	Author, year Quality	Pop cat	ADL or ADL, (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SE)	IG n at FU	IG FU mean (SE)	IG mean change (SE or 95% CI) from BL	CG BL mean (SE)	CG n at FU	CG FU mean (SE)	CG mean change (SE or 95% CI) from BL	Between group difference, p-value
Galantamine	Rockwood, 2001[208] Fair-Good	Dem	ADL/IADL (DAD, 0-100, ↑)	IG1	3	73.0 (1.91)	241	NR	-0.4 (0.76)	69.1 (1.42)	123	NR	-5.2 (1.18)	NR, <0.001
Galantamine	Rockwood, 2006[207] Fair	Dem	ADL/IADL (DAD, 0-100, ↑)	IG1	4	76.4 (19.7)‡	NR	NR	NR	70.6 (21.4)‡	NR	NR	NR	ES=0.28, 0.13
Galantamine	Tariot, 2000[209] Fair-Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	5	51.9 (1.0)	253	NR	-1.5 (0.6)	52.3 (0.9)	262	NR	-3.8 (0.6)	NR, <0.01
Galantamine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG2	5	51.6 (0.9)	255	NR	-0.7 (0.5)	52.3 (0.9)	262	NR	-3.8 (0.6)	NR, <0.001
Galantamine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG3	5	54.2 (1.2)	129	NR	-3.2 (0.8)	52.3 (0.9)	262	NR	-3.8 (0.6)	NR
Galantamine	Wilcock, 2000[210] Fair-Good	Dem	ADL/IADL (DAD, 0-100, ↑)	IG1	6	69.9 (21.4)‡	212	NR	-3.2 (1.02)	66.6 (22.5)‡	210	NR	-6.0 (1.08)	MDC (95% CI)=2.8 (-0.6, 6.1), 0.1
Galantamine		Dem	ADL/IADL (DAD, 0-100, ↑)	IG2	6	69.6 (20.6)‡	214	NR	-2.5 (1.07)	66.6 (22.5)‡	210	NR	-6.0 (1.08)	MDC (95% CI)=3.4 (0.1, 6.7), <0.05
Galantamine	Wilkinson, 2001[211] Fair-Good	Dem	ADL/IADL (PDS, D)	IG1	3	NA	56	50 (89.3)¶	NR	NA	87	65 (74.7)¶	NR	NR
Galantamine		Dem	ADL/IADL (PDS, D)	IG2	3	NA	54	42 (77.8)¶	NR	NA	87	65 (74.7)¶	NR	NR
Galantamine		Dem	ADL/IADL (PDS, D)	IG3	3	NA	88	72 (81.8)¶	NR	NA	87	65 (74.7)¶	NR	NR
Rivastigmine	Agid, 1998[212] Fair-Good	Dem	ADL (NOSGER ADL subscale, 1-5, ↓)	IG1	3	NR	103	NR	-0.1 (2.1)‡	NR	117	NR	0.1 (2.7)‡	NR
Rivastigmine		Dem	ADL (NOSGER ADL subscale, 1-5, ↓)	IG2	3	NR	111	NR	0.2 (2.8)‡	NR	117	NR	0.1 (2.7)‡	NR
Rivastigmine		Dem	ADL (NOSGER ADL subscale, 1-5, ↓)	IG1	3	NR	103	NR	-0.7 (3.5)‡	NR	117	NR	-0.2 (3.3)‡	NR
Rivastigmine	Agid, 1998[212] Fair-Good	Dem	ADL (NOSGER ADL subscale, 1-5, ↓)	IG2	3	NR	111	NR	0.0 (3.3)‡	NR	117	NR	-0.2 (3.3)‡	NR
Rivastigmine	Ballard, 2008[213] Fair	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	46.7 (17.7)‡	365	NR	-0.1 (0.59)	46.4 (17.2)‡	345	NR	-0.7 (0.60)	MDC (95% CI)=0.6, NS
Rivastigmine	Corey-Bloom, 1998[214] Fair-Good	Dem	ADL/IADL (PDS, 0-100, ↑)	IG1	3	NR	169	NR	-0.7 (NR)	NR	216	NR	-1.9 (NR)	NR
Rivastigmine		Dem	ADL/IADL (PDS, 0-100, ↑)	IG1	4	NR	157	NR	-0.6 (NR)	NR	201	NR	-4.0 (NR)	NR, <0.05

Appendix E Table 4. AChEIs and Memantine: Detailed Results for Physical Function Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	ADL or ADL, (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SE)	IG n at FU	IG FU mean (SE)	IG mean change (SE or 95% CI) from BL	CG BL mean (SE)	CG n at FU	CG FU mean (SE)	CG mean change (SE or 95% CI) from BL	Between group difference, p-value
Rivastigmine		Dem	ADL/IADL (PDS, 0-100, ↑)	IG1	6	NR	231	NR	-1.52 (-2.85, -0.19)	NR	234	NR	-4.90 (-6.22, -3.58)	MDC (95% CI)=3.38 (1.51, 5.25), <0.001
Rivastigmine		Dem	ADL/IADL (PDS, 0-100, ↑)	IG2	3	NR	223	NR	-3.6 (NR)	NR	216	NR	-1.9 (NR)	NR
Rivastigmine		Dem	ADL/IADL (PDS, 0-100, ↑)	IG2	4	NR	208	NR	-3.4 (NR)	NR	201	NR	-4.0 (NR)	NR
Rivastigmine		Dem	ADL/IADL (PDS, 0-100, ↑)	IG2	6	NR	233	NR	-5.19 (-6.52, -3.86)	NR	234	NR	-4.90 (-6.22, -3.58)	NR
Rivastigmine		Dem	ADL/IADL (PDS, D)	IG1	6	NA	145	36 (24.8)[#]	NR	NA	192	29 (15.1)[#]	NR	NR, 0.006
Rivastigmine		Dem	ADL/IADL (PDS, D)	IG1	6	NA	194	NR[#]	NR	NA	192	29 (15.1)[#]	NR	NS
Rivastigmine	Feldman, 2007[215] Fair	Dem	ADL/IADL (PDS, 0-100, ↑)	IG1	6	49.2 (19.8)[‡]	225	NR	-1.5 (11.3)[‡]	49.0 (19.6)[‡]	221	NR	-4.9 (11.2)[‡]	NR
Rivastigmine		Dem	ADL/IADL (PDS, 0-100, ↑)	IG2	6	48.7 (19.5)[‡]	227	NR	-2.6 (11.1)[‡]	49.0 (19.6)[‡]	221	NR	-4.9 (11.2)[‡]	NR
Rivastigmine	Mok, 2007[217] Fair	Dem	IADL (Lawton and Brody IADL, 0-8, ↑)	IG1	6	2.3 (0.7)[‡]	20	2.3 (0.5)[‡]	NR	2.3 (0.6)[‡]	19	2.2 (0.8)[‡]	NR	NR, 0.299
Rivastigmine	Rosler, 1999[218] Fair-Good	Dem	ADL/IADL (PDS, 0-100, ↑)	IG1	3	NR	191	NR	0.48 (NR)	NR	226	NR	0.12 (NR)	NS
Rivastigmine		Dem	ADL/IADL (PDS, 0-100, ↑)	IG1	4	NR	179	NR	0.08 (NR)	NR	218	NR	-0.99 (NR)	NS
Rivastigmine		Dem	ADL/IADL (PDS, 0-100, ↑)	IG1	6	NR	198	NR	0.5 (-1.32, 2.52)	NR	223	NR	-2.23 (-4.02, -0.38)	NR, <0.05
Rivastigmine		Dem	ADL/IADL (PDS, 0-100, ↑)	IG2	3	NR	226	NR	-0.90 (NR)	NR	226	NR	0.12 (NR)	NS
Rivastigmine		Dem	ADL/IADL (PDS, 0-100, ↑)	IG2	4	NR	219	NR	-1.78 (NR)	NR	218	NR	-0.99 (NR)	NS
Rivastigmine	Rosler, 1999[218] Fair-Good	Dem	ADL/IADL (PDS, 0-100, ↑)	IG2	6	NR	225	NR	-3.31 (-5.10, -1.50)	NR	223	NR	-2.23 (-4.02, -0.38)	NR, >0.05
Rivastigmine	Winblad, 2007[219] Fair	Dem	ADL/IADL (PDS, D)	IG1	6	NA	198	66 (33.3)[#]	NR	NA	223	45 (20.2)[#]	NR	NR, <0.01
Rivastigmine	Winblad, 2007[219] Fair	Dem	ADL/IADL (PDS, D)	IG2	6	NA	225	45 (20.0)[#]	NR	NA	223	45 (20.0)[#]	NR	NR, >0.05
Rivastigmine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	49.3 (15.8)[‡]	254	NR	-0.5 (9.5)	49.2 (16.0)[‡]	281	NR	-2.3 (9.4)[‡]	NR, 0.04
Rivastigmine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG2	6	47.6 (15.7)[‡]	263	NR	0.0 (11.6)	49.2 (16.0)[‡]	281	NR	-2.3 (9.4)[‡]	NR, 0.02

Appendix E Table 4. AChEIs and Memantine: Detailed Results for Physical Function Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	ADL or ADL, (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SE)	IG n at FU	IG FU mean (SE)	IG mean change (SE or 95% CI) from BL	CG BL mean (SE)	CG n at FU	CG FU mean (SE)	CG mean change (SE or 95% CI) from BL	Between group difference, p-value
Rivastigmine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG3	6	50.1 (16.3)‡	247	NR	-0.1 (9.1)	49.2 (16.0)‡	281	NR	-2.3 (9.4)‡	NR, 0.01
Memantine	Bakchine, 2008[220] Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	3	NR	268	NR	-0.67 (NR)	NR	135	NR	-0.19 (NR)	MDC (95% CI)=-0.48 (-1.8, 0.85), 0.480
Memantine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	NR	267	NR	-1.99 (NR)	NR	134	NR	-2.08 (NR)	MDC (95% CI)=0.09 (-1.52, 1.70), 0.912
Memantine	Choi, 2011[ll221] Fair	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	4	51.0 (13.8)‡	84	NR	-1.4 (7.9)	52.4 (15.9)‡	74	NR	-2.4 (8.5)‡	NR, 0.50
Memantine	Dysken, 2014[ll222] Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	12	57.3 (14.2)‡	119	NR	-7.08† (-9.39, -4.64)	56.8 (13.7)‡	112	NR	-8.14† (-10.5, -5.73)	NR
Memantine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	18	57.3 (14.2)‡	95	NR	-9.39† (-12.1, -6.55)	56.8 (13.7)‡	96	NR	-10.2† (-13.0, -7.40)	NR
Memantine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	24	57.3 (14.2)‡	80	NR	-14.0† (-17.4, -10.7)	56.8 (13.7)‡	77	NR	-16.2† (-19.6, -12.8)	NR
Memantine	Dysken, 2014[ll222] Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	30	57.3 (14.2)‡	64	NR	-18.4† (-22.1, -14.4)	56.8 (13.7)‡	54	NR	-19.7† (-23.7, -15.6)	NR
Memantine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	36	57.3 (14.2)‡	38	NR	-18.9† (-23.5, -14.0)	56.8 (13.7)‡	33	NR	-24.8† (-29.7, -19.9)	NR
Memantine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	42	57.3 (14.2)‡	38	NR	-23.6† (-28.7, -18.3)	56.8 (13.7)‡	33	NR	-28.1† (-33.5, -22.7)	NR
Memantine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	48	57.3 (14.2)‡	142	NR	-14.98† (1.10)	56.8 (13.7)‡	140	NR	-16.96† (1.11)	MDC (95% CI)=1.98 (-0.24, 4.20), 0.40
Memantine	Dysken, 2014[ll222] Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	57.3 (14.2)‡	139	NR	-2.47† (-4.30, -0.59)	56.8 (13.7)‡	135	NR	-4.54† (-6.42, -2.68)	NR
Memantine	Orgogozo, 2002[225] Fair-Good	Dem	ADL (NOSGER ADL subscale, 1-5, ↓)	IG1	6	NR	93	NR	0.40 (NR)	NR	95	NR	0.19 (NR)	NR, 0.931
Memantine		Dem	ADL (NOSGER ADL subscale, 1-5, ↓)	IG1	6	NR	116	NR	1.05 (NR)	NR	118	NR	0.34 (NR)	NR, 0.321
Memantine	Peskind, 2006[226] Fair-Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	57.2 (14.77)‡	196	NR	-2.07† (7.14)‡	56.2 (13.11)‡	197	NR	-1.77† (7.18)‡	NR, 0.63
Memantine	Peters, 2015[ll227] Fair	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	12	62.1 (10.5)‡	94	NR	-6.83 (1.33)‡	62.1 (12.9)‡	96	NR	-6.16 (1.34)‡	NR, 0.719

Appendix E Table 4. AChEIs and Memantine: Detailed Results for Physical Function Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	ADL or ADL, (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SE)	IG n at FU	IG FU mean (SE)	IG mean change (SE or 95% CI) from BL	CG BL mean (SE)	CG n at FU	CG FU mean (SE)	CG mean change (SE or 95% CI) from BL	Between group difference, p-value
Memantine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	4	62.1 (10.5)‡	77	NR	-0.92 (0.90)‡	62.1 (12.9)‡	74	NR	-1.40 (0.92)‡	NS
Memantine		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	62.1 (10.5)‡	72	NR	-2.53 (1.09)‡	62.1 (12.9)‡	77	NR	-3.38 (1.05)‡	NS
Memantine	Porsteinsson, 2008[228] Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	54.7 (14.44)‡	214	51.8 (15.89)‡	NR	54.8 (13.08)‡	213	52.0 (15.70)‡	NR	MDC (95% CI)=-0.2 (-1.6, 1.3), 0.816

* Least squares mean
† Least squares mean change
‡ Standard deviation
§ Range
‖ New study
¶ Number (%) of participants demonstrating no change, improvement, or much improvement on PDS
# Number (%) of participants demonstrating clinically meaningful improvement (≥10% improvement in PDS total score)

Abbreviations: ADL = Activities of Daily Living; ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living 23 items; ADFACS = Alzheimer's Disease Functional Assessment and Change Scale; BL = baseline; CG = control group; CI = confidence interval; D = dichotomized; DAD = Disability Assessment for Dementia scale; Dem = dementia; ES = effect size; FU = followup; IADL = Instrumental Activities of Daily Living; IDDD = Interview for Deterioration in Daily Living Activities in Dementia; IG = intervention group; Int arm = intervention arm; MCI = mild cognitive impairment; MDC = mean difference in change; mo. = months; PDS = Progressive Deterioration Scale; Pop cat = population category; NA = not applicable; NOSGER = Nurses' Observation Scale for Geriatric Patients scale; NR = not reported; NS = not statistically significant; PSMS = Physical Self-Maintenance Scale; SE = standard error

Appendix E Table 5. AChEIs and Memantine: Detailed Results for Mental Health and Neuropsychiatric Symptom Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Symptom (Instrument, range†)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Donepezil	Doody, 2009[186] Fair	MCI	NPS (NPI-12, 0-144)	IG1	11	4.0 (7.3)	379	NR	1.8 (0.5)‡	3.4 (5.8)	378	NR	3.4 (5.8)‡	NS
Donepezil	Feldman, 2001[187] Fair-Good	Dem	NPS (NPI-12, 0-144)	IG1	3	19.55 (1.48)‡	127	NR	-4.69§ (1.22)‡	19.30 (1.45)	132	NR	-3.06§ (1.14)‡	NR
Donepezil		Dem	NPS (NPI-12, 0-144)	IG1	4	19.55 (1.48)‡	122	NR	-3.86§ (1.39)‡	19.30 (1.45)	126	NR	-0.47§ (1.29)‡	NR
Donepezil		Dem	NPS (NPI-12, 0-144)	IG1	6	19.55 (1.48)‡	138	NR	-4.6§ (1.24)‡	19.30 (1.45)	144	NR	1.0§ (1.19)‡	MDC=-5.64, 0.0005
Donepezil	Holmes, 2004[188] Fair-Good	Dem	NPS (NPI-10, 0-120)	IG1	6	14.3 (1.4)‡	41	NR	-2.9 (1.6)‡	15.1 (1.8)‡	55	NR	3.3 (2.1)‡	NR, 0.02
Donepezil	Ikeda, 2015*[189] Fair	Dem	NPS (NPI-10, 0-120)	IG1	3	16.6 (11.7)	49	NR	-5.5 (1.4)‡	20.5 (15.0)	44	NR	-6.4 (1.5)‡	MDC (95% CI)=0.9 (-3.1, 4.9), 0.660
Donepezil		Dem	NPS (NPI-10, 0-120)	IG2	3	18.9 (15.3)	45	NR	-3.3 (1.4)‡	20.5 (15.0)	44	NR	-6.4 (1.5)‡	MDC (95% CI)=3.0 (-1.0, 7.1), 0.143
Donepezil	Mori, 2012[193] Fair	Dem	NPS (NPI-10, 0-120)	IG1	3	19.5 (12.8)	35	NR	-8.0 (12.8)	18.3 (8.9)	32	NR	0.3 (17.5)	MDC (95% CI)=-8.3 (-15.8, -0.9), 0.019
Donepezil		Dem	NPS (NPI-10, 0-120)	IG2	3	14.0 (8.3)	32	NR	-5.5 (6.7)	18.3 (8.9)	32	NR	0.3 (17.5)	MDC (95% CI)=-5.8 (-12.4, 0.8), 0.047
Donepezil		Dem	NPS (NPI-10, 0-120)	IG3	3	20.7 (12.8)	35	NR	-3.9 (22.0)	18.3 (8.9)	32	NR	0.3 (17.5)	MDC (95% CI)=-4.2 (-13.9, 5.6), 0.602
Donepezil	Tune, 2003[199] Fair-Good	Dem	NPS (NPI-12, 0-144)	IG1	3	18.36 (12.40)	14	NR	0.91§ (14.50)	8.79 (9.79)	13	NR	-1.52§ (13.30)	NR (95% CI)=NR (-7.50, 12.37), 0.652
Donepezil		Dem	NPS (NPI-12, 0-144)	IG1	6	18.36 (12.40)	14	NR	5.40§ (17.80)	8.79 (9.79)	13	NR	2.65§ (14.00)	NR (95% CI)=NR (-9.87, 15.39), 0.688
Galantamine	Brodaty, 2005[203] Fair-Good	Dem	NPS (NPI-12, 0-144)	IG1	6	12.6 (NR)	242	NR	-0.9 (0.73)‡	10.3 (NR)	258	NR	0.6 (0.62)‡	NR (95% CI)=NR (-3.42, 0.23), 0.102
Galantamine		Dem	NPS (NPI-12, 0-144)	IG2	6	11.2 (NR)	245	NR	-0.6 (0.66)‡	10.3 (NR)	258	NR	0.6 (0.62)‡	NR (95% CI)=NR (-1.85, 1.82), 0.941
Galantamine	Erkinjuntti, 2002[204] Fair-Good	Dem	NPS (NPI-10, 0-120)	IG1	6	12.2 (12.98)	279	NR	-1.2 (0.6)‡	11.4 (11.27)	154	NR	1.0 (0.9)‡	MDC=-2.2, 0.0164
Galantamine	Rockwood, 2001[208] Fair-Good	Dem	NPS (NPI-10, 0-120)	IG1	3	9.2 (0.66)‡	241	NR	-0.3 (0.70)‡	9.4 (1.01)‡	123	NR	0.5 (0.65)‡	NS
Galantamine	Tariot, 2000[209] Fair-Good	Dem	NPS (NPI-10, 0-120)	IG1	5	11.9 (0.8)‡	253	NR	0.0 (0.8)‡	11.0 (0.7)‡	262	NR	2.0 (0.7)‡	NR, 0.03
Galantamine	Tariot, 2000[209] Fair-Good	Dem	NPS (NPI-10, 0-120)	IG2	5	12.4 (0.8)‡	255	NR	-0.1 (0.7)‡	11.0 (0.7)‡	262	NR	2.0 (0.7)‡	NR, 0.04
Galantamine		Dem	NPS (NPI-10, 0-120)	IG3	5	12.9 (1.2)‡	129	NR	2.3 (1.0)‡	11.0 (0.7)‡	262	NR	2.0 (0.7)‡	NR

Appendix E Table 5. AChEIs and Memantine: Detailed Results for Mental Health and Neuropsychiatric Symptom Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Symptom (Instrument, range†)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Rivastigmine	Ballard, 2008[213] Fair	Dem	NPS (NPI-12, 0-144)	IG1	6	13.4 (12.5)	364	NR	-1.4 (0.63)‡	12.9 (11.5)	342	NR	-1.8 (0.64)‡	MDC=0.4, NS
Rivastigmine	McKeith, 2000[216] Fair-Good	Dem	NPS (NPI-10, 0-120)	IG1	5	23.2 (15.0)	47	NR	-5.0 (16.2)	20.2 (14.2)	53	NR	-1.2 (10.7)	MDC (95% CI)=-3.8 (-1.6, 9.2), 0.048
Rivastigmine	Mok, 2007[217] Fair	Dem	Anxiety (NPI, Anxiety subscale, 0-12)	IG1	6	0.8 (1.9)	20	0.3 (0.7)	NR	0.2 (0.5)	19	0.2 (0.7)	NR	NR, 0.346
Rivastigmine		Dem	NPS (NPI-12, 0-144)	IG1	6	15.0 (14.6)	20	11.4 (9.4)	NR	9.5 (6.5)	19	10.4 (11.3)	NR	NR, 0.282
Rivastigmine	Winblad, 2007[219] Fair	Dem	NPS (NPI-12, 0-144)	IG1	6	15.1 (14.1)	253	NR	-2.2 (11.9)	14.9 (15.7)	281	NR	-1.7 (13.8)	NR, 0.51
Rivastigmine		Dem	NPS (NPI-12, 0-144)	IG2	6	15.1 (13.4)	263	NR	-2.3 (13.3)	14.9 (15.7)	281	NR	-1.7 (13.8)	NR, 0.69
Rivastigmine		Dem	NPS (NPI-12, 0-144)	IG3	6	13.9 (14.1)	248	NR	-1.7 (11.5)	14.9 (15.7)	281	NR	-1.7 (13.8)	NR, 0.74
Memantine	Bakchine, 2008[220] Good	Dem	NPS (NPI-12, 0-144)	IG1	3	NR	268	NR	-1.37 (NR)	NR	135	NR	-1.02 (NR)	MDC (95% CI)=-0.35 (-1.96, 1.26), 0.671
Memantine		Dem	NPS (NPI-12, 0-144)	IG1	6	NR	267	NR	-1.45 (NR)	NR	134	NR	-2.73 (NR)	MDC (95% CI)=1.28 (-0.5, 3.05), 0.159
Memantine	Choi, 2011*[221] Fair	Dem	NPS (NPI-12, 0-144)	IG1	4	14.7 (18.4)	84	NR	1.2 (10.8)	13.3 (18.7)	74	NR	1.0 (15.8)	NR, 0.88
Memantine	Dysken, 2014*[222] Good	Dem	NPS (NPI-12, 0-144)	IG1	6	8.0‖ (NR)	139	NR	-0.26§ (-2.26, 1.89)¶	8.0‖ (NR)	135	NR	0.47§ (-1.62, 2.57)¶	NR
Memantine		Dem	NPS (NPI-12, 0-144)	IG1	12	8.0‖ (NR)	119	NR	0.26§ (-2.07, 2.70)¶	8.0‖ (NR)	112	NR	1.08§ (-1.36, 3.53)¶	NR
Memantine		Dem	NPS (NPI-12, 0-144)	IG1	18	8.0‖ (NR)	94	NR	1.14§ (-1.62, 4.00)¶	8.0‖ (NR)	96	NR	4.05§ (1.26, 6.87)¶	NR
Memantine		Dem	NPS (NPI-12, 0-144)	IG1	24	8.0‖ (NR)	80	NR	4.24§ (0.78, 7.81)¶	8.0‖ (NR)	75	NR	3.59§ (0.004, 7.19)¶	NR
Memantine		Dem	NPS (NPI-12, 0-144)	IG1	30	8.0‖ (NR)	64	NR	2.57§ (-0.73, 5.98)¶	8.0‖ (NR)	55	NR	1.68§ (-1.88, 5.21)¶	NR
Memantine		Dem	NPS (NPI-12, 0-144)	IG1	36	8.0‖ (NR)	45	NR	3.17 (-0.83, 7.31)¶	8.0‖ (NR)	41	NR	0.60§ (-3.63, 4.83)¶	NR
Memantine		Dem	NPS (NPI-12, 0-144)	IG1	42	8.0‖ (NR)	38	NR	3.58§ (-1.75, 9.01)¶	8.0‖ (NR)	33	NR	3.63§ (-2.01, 9.31)¶	NR
Memantine	Dysken, 2014*[222] Good	Dem	NPS (NPI-12, 0-144)	IG1	48	8.0‖ (NR)	142	NR	1.87§ (1.00)‡	8.0‖ (NR)	140	NR	2.26§ (1.01)‡	MDC (95% CI)=-0.39 (-2.47, 1.70), 0.94

Appendix E Table 5. AChEIs and Memantine: Detailed Results for Mental Health and Neuropsychiatric Symptom Outcomes, by Medication Type

Medication	Author, year Quality	Pop cat	Symptom (Instrument, range†)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Memantine	Herrmann, 2013*[224] Fair	Dem	NPS (NPI-12, 0-144)	IG1	6	30.94 (1.17)‡	159	NR	-3.90 (1.24)‡	29.18 (1.03)‡	165	NR	-5.13 (1.23)‡	MDC (95% CI)=1.23 (-1.75, 4.21), 0.42
Memantine	Peskind, 2006[226] Fair-Good	Dem	NPS (NPI-12, 0-144)	IG1	3	11.5 (13.20)	183	NR	-1.70§ (13.66)	12.2 (13.00)	179	NR	0.20§ (13.78)	LSM change (95% CI)=-2.4 (-4.7, -0.2), 0.035
Memantine		Dem	NPS (NPI-12, 0-144)	IG1	6	11.5 (13.20)	196	NR	-1.37§ (13.30)	12.2 (13.00)	198	NR	0.97§ (13.50)	LSM change (95% CI)=-2.34 (-4.5, -0.18), 0.03
Memantine	Peters, 2015*[227] Fair	Dem	NPS (NPI-12, 8-96)	IG1	12	NR	94	NR	NR	NR	96	NR	NR	NR, 0.106
Memantine	Porsteinsson, 2008[227] Good	Dem	NPS (NPI-12, 0-144)	IG1	6	11.8 (13.11)	212	12.9 (14.48)	NR	12.3 (13.28)	209	12.6 (14.56)	NR	MDC (95% CI)=0.3 (-1.7, 2.4), 0.743
Memantine	Wilkinson, 2012[231] Fair	Dem	NPS (NPI-12, 0-144)	IG1	12	13.1 (12.8)	103	NR	NR	12.8 (12.4)	114	NR	NR	MDC (SE)=0.56 (1.19), NS

* New study
† Lower scores indicate better outcomes for all instruments
‡ Standard error
§ Least squares mean change
‖ Median
¶ 95% CI

Abbreviations: BL = baseline; CG = control group; CI = confidence interval; Dem = dementia; FU = followup; IG = intervention group; Int arm = intervention arm; LSM = least squares mean; MCI = mild cognitive impairment; MDC = mean difference in change; mo. = months; NPI-10 = Neuropsychiatric Inventory-10 item; NPI-12 = Neuropsychiatric Inventory-12 item; NPS = Composite neuropsychiatric symptoms; NR = not reported; NS = not statistically significant; SD = standard deviation; SE = standard error

Appendix E Table 6. AChEIs and Memantine: Detailed Results for Harms, by Medication Type

Medication	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
Donepezil	Black, 2003[184] Fair-Good	Adverse events	IG1	6	206	195 (94.7)	199	176 (88.4)	NR, 0.03
Donepezil		Adverse events	IG2	6	198	176 (88.9)	199	176 (88.4)	NR, 1.0
Donepezil		Serious adverse events	IG1	6	206	45 (21.8)	199	30 (15.1)	NR
Donepezil		Serious adverse events	IG2	6	198	32 (16.2)	199	30 (15.1)	NR
Donepezil		Withdrawals due to adverse events	IG1	6	206	45 (21.8)	199	22 (11.1)	NR
Donepezil		Withdrawals due to adverse events	IG2	6	198	22 (11.1)	199	22 (11.1)	NR
Donepezil	Burns, 1999[185] Fair-Good	Serious adverse events	IG1	6	273	24 (8.8)	274	25 (9.1)	NR
Donepezil		Serious adverse events	IG2	6	271	24 (8.9)	274	25 (9.1)	NR
Donepezil		Withdrawals due to adverse events	IG1	6	273	50 (18.3)	274	27 (9.9)	NR
Donepezil		Withdrawals due to adverse events	IG2	6	271	24 (8.9)	274	27 (9.9)	NR
Donepezil	Doody, 2009[186] Fair	Adverse events	IG1	11	391	318 (81.3)	387	267 (69.0)	NR
Donepezil		Serious adverse events	IG1	11	391	48 (12.3)	387	41 (10.6)	NR
Donepezil		Withdrawals due to adverse events	IG1	11	391	72 (18.4)	387	32 (8.3)	NR
Donepezil	Feldman, 2001[187] Fair-Good	Adverse events	IG1	6	144	120 (83.3)	146	117 (80.1)	NR
Donepezil		Serious adverse events	IG1	6	144	19 (13.2)	146	18 (12.3)	NR
Donepezil		Withdrawals due to adverse events	IG1	6	144	12 (8.3)	146	9 (6.2)	NR
Donepezil	Holmes, 2004[188] Fair-Good	Adverse events	IG1	6	41	3 (7.3)	55	0 (0.0)	NR
Donepezil	Ikeda, 2015*[189] Fair	Adverse events	IG1	3	49	34 (69.4)	46	31 (67.4)	NR
Donepezil		Adverse events	IG2	3	47	30 (63.8)	46	31 (67.4)	NR

Appendix E Table 6. AChEIs and Memantine: Detailed Results for Harms, by Medication Type

Medication	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
Donepezil		Serious adverse events	IG1	3	49	1 (2.0)	46	3 (6.5)	NR
Donepezil		Serious adverse events	IG2	3	47	4 (8.5)	46	3 (6.5)	NR
Donepezil		Withdrawals due to adverse events	IG1	3	49	2 (4.1)	46	5 (10.9)	NR
Donepezil		Withdrawals due to adverse events	IG2	3	47	10 (21.3)	46	5 (10.9)	NR
Donepezil	Krishnan, 2003[190]	Adverse events	IG1	6	34	32 (94.1)	33	28 (84.8)	NS
Donepezil	Fair-Good	Withdrawals due to adverse events	IG1	6	34	0 (0.0)	33	1 (3.0)	NR
Donepezil	Mazza, 2006[191] Fair-Good	Adverse events	IG1	6	25	4 (16.0)	26	0 (0.0)	NR
Donepezil	Mohs, 2001[192] Fair	Serious adverse events	IG1	12	214	26 (12.1)	217	19 (8.8)	NR
Donepezil		Withdrawals due to adverse events	IG1	12	214	20 (9.3)	217	12 (5.5)	NR
Donepezil	Mori, 2012[193] Fair	Adverse events	IG1	3	37	32 (86.5)	34	24 (70.6)	NR
Donepezil		Adverse events	IG2	3	33	27 (81.8)	34	24 (70.6)	NR
Donepezil		Adverse events	IG3	3	35	24 (68.6)	34	24 (70.6)	NR
Donepezil		Serious adverse events	IG1	3	37	4 (10.8)	34	2 (5.9)	NR
Donepezil		Serious adverse events	IG2	3	33	2 (6.1)	34	2 (5.9)	NR
Donepezil		Serious adverse events	IG3	3	35	2 (5.7)	34	2 (5.9)	NR
Donepezil		Withdrawals due to adverse events	IG1	3	37	3 (8.1)	34	4 (11.8)	NR
Donepezil		Withdrawals due to adverse events	IG2	3	33	1 (3.0)	34	4 (11.8)	NR
Donepezil	Mori, 2012[193] Fair	Withdrawals due to adverse events	IG3	3	35	3 (8.6)	34	4 (11.8)	NR

Appendix E Table 6. AChEIs and Memantine: Detailed Results for Harms, by Medication Type

Medication	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
Donepezil	Petersen, 2005[194] Fair	Adverse events	IG1	36	253	221†	259	64†	NR, <0.01
Donepezil	Rogers, 1996[196] Fair-Good	Adverse events	IG1	3	39	26 (66.7)	40	26 (65.0)	NR
Donepezil		Adverse events	IG2	3	40	27 (67.5)	40	26 (65.0)	NR
Donepezil		Adverse events	IG3	3	42	27 (64.3)	40	26 (65.0)	NR
Donepezil		Withdrawals due to adverse events	IG1	3	39	3 (7.7)	40	2 (5.0)	NR
Donepezil		Withdrawals due to adverse events	IG2	3	40	2 (5.0)	40	2 (5.0)	NR
Donepezil		Withdrawals due to adverse events	IG3	3	42	5 (11.9)	40	2 (5.0)	NR
Donepezil	Rogers, 1998[195] Fair-Good	Adverse events	IG1	3	158	124 (78.5)	153	106 (69.3)	NR
Donepezil		Adverse events	IG2	3	157	106 (67.5)	153	106 (69.3)	NR
Donepezil		Serious adverse events	IG1	3	158	6 (3.8)	153	7 (4.6)	NR
Donepezil		Serious adverse events	IG2	3	157	6 (3.8)	153	7 (4.6)	NR
Donepezil		Withdrawals due to adverse events	IG1	3	158	16 (10.1)	153	3 (2.0)	NR
Donepezil		Withdrawals due to adverse events	IG2	3	157	7 (4.5)	153	3 (2.0)	NR
Donepezil	Salloway, 2004[197] Fair-Good	Adverse events	IG1	6	132	116 (87.9)	137	100 (73.0)	NR, ≤0.03
Donepezil		Serious adverse events	IG1	6	133	5 (3.8)	137	6 (4.4)	NR
Donepezil		Withdrawals due to adverse events	IG1	6	133	29 (21.8)	137	10 (7.3)	NR
Donepezil	Seltzer, 2004[198] Fair-Good	Adverse events	IG1	6	96	67 (69.8)	57	37 (64.9)	NR
Donepezil		Serious adverse events	IG1	6	96	5 (5.2)	57	3 (5.3)	NR
Donepezil	Seltzer, 2004[198] Fair-Good	Withdrawals due to adverse events	IG1	6	96	15 (15.6)	57	5 (8.8)	NR

Appendix E Table 6. AChEIs and Memantine: Detailed Results for Harms, by Medication Type

Medication	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
Donepezil	Tune, 2003[199] Fair-Good	Withdrawals due to adverse events	IG1	6	14	0 (0.0)	14	0 (0.0)	NR
Donepezil	Wilkinson, 2003[200] Fair-Good	Adverse events	IG1	6	215	197 (91.6)	193	167 (86.5)	NR
Donepezil		Adverse events	IG2	6	208	188 (90.4)	193	167 (86.5)	NR
Donepezil		Serious adverse events	IG1	6	215	31 (14.4)	193	32 (16.6)	NR
Donepezil		Serious adverse events	IG2	6	208	28 (13.5)	193	32 (16.6)	NR
Donepezil		Withdrawals due to adverse events	IG1	6	215	35 (16.3)	193	17 (8.8)	NR
Donepezil		Withdrawals due to adverse events	IG2	6	208	21 (10.1)	193	17 (8.8)	NR
Donepezil	Winblad, 2001[201] Fair-Good	Adverse events	IG1	12	142	116 (81.7)	144	109 (75.7)	NR
Donepezil		Serious adverse events	IG1	12	142	35 (24.6)	144	20 (13.9)	NR
Donepezil		Withdrawals due to adverse events	IG1	12	142	10 (7.0)	144	9 (6.3)	NR
Galantamine	Auchus, 2007[202] Fair	Adverse events	IG1	6	396	301 (76.0)	390	278 (71.3)	NR
Galantamine		Serious adverse events	IG1	6	396	80 (20.2)	390	72 (18.5)	NR
Galantamine		Withdrawals due to adverse events	IG1	6	396	54 (13.6)	390	27 (6.9)	NR
Galantamine	Brodaty, 2005[203] Fair-Good	Adverse events	IG1	6	326	235 (72.1)	320	224 (70.0)	NR
Galantamine		Adverse events	IG2	6	319	253 (79.3)	320	224 (70.0)	NR
Galantamine		Serious adverse events	IG1	6	326	3 (0.9)	320	3 (0.9)	NR
Galantamine		Serious adverse events	IG2	6	319	3 (0.9)	320	3 (0.9)	NR
Galantamine	Brodaty, 2005[203] Fair-Good	Withdrawals due to adverse events	IG1	6	326	24 (7.4)	320	15 (4.7)	NR

Appendix E Table 6. AChEIs and Memantine: Detailed Results for Harms, by Medication Type

Medication	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
Galantamine		Withdrawals due to adverse events	IG2	6	319	28 (8.8)	320	15 (4.7)	NR
Galantamine	Erkinjuntti, 2002[204] Fair-Good	Adverse events	IG1	6	396	330 (83.3)	196	133 (67.9)	NR
Galantamine		Withdrawals due to adverse events	IG1	6	396	78 (19.7)	196	16 (8.2)	NR
Galantamine	Hager, 2014*[205] Fair	Adverse events	IG1	24	1024	553 (54.0)	1021	496 (48.6)	NR
Galantamine		Serious adverse events	IG1	24	1024	129 (12.6)	1021	123 (12.0)	NR
Galantamine		Withdrawals due to adverse events	IG1	24	1024	87 (8.5)	1021	66 (6.5)	NR
Galantamine	Raskind, 2000[206] Fair-Good	Adverse events	IG1	6	212	195 (92.0)	213	168 (78.9)	NR
Galantamine		Adverse events	IG2	6	211	195 (92.4)	213	168 (78.9)	NR
Galantamine		Serious adverse events	IG1	6	212	NR	213	NR	NS
Galantamine		Serious adverse events	IG2	6	211	NR	213	NR	NS
Galantamine		Withdrawals due to adverse events	IG1	6	212	49 (23.1)	213	16 (7.5)	NR
Galantamine		Withdrawals due to adverse events	IG2	6	211	67 (31.8)	213	16 (7.5)	NR
Galantamine	Rockwood, 2001[208] Fair-Good	Adverse events	IG1	3	261	225 (86.2)	125	79 (63.2)	NR
Galantamine		Serious adverse events	IG1	3	261	21 (8.0)	125	8 (6.4)	NR
Galantamine		Withdrawals due to adverse events	IG1	3	261	66 (25.3)	125	5 (4.0)	NR
Galantamine	Rockwood, 2006[207] Fair	Adverse events	IG1	4	64	54 (84.4)	66	41 (62.1)	NR
Galantamine		Serious adverse events	IG1	4	64	5 (7.8)	66	10 (15.2)	NR
Galantamine	Rockwood, 2006[207] Fair	Withdrawals due to adverse events	IG1	4	64	5 (7.8)	66	2 (3.0)	NR
Galantamine	Tariot, 2000[209] Fair-Good	Adverse events	IG1	5	273	219 (80.2)	286	206 (72.0)	NR

Appendix E Table 6. AChEIs and Memantine: Detailed Results for Harms, by Medication Type

Medication	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
Galantamine		Adverse events	IG2	5	279	206 (73.8)	286	206 (72.0)	NR
Galantamine		Adverse events	IG3	5	140	106 (75.7)	286	206 (72.0)	NR
Galantamine		Serious adverse events	IG1	5	273	35 (12.8)	286	31 (10.8)	NR
Galantamine		Serious adverse events	IG2	5	279	28 (10.0)	286	31 (10.8)	NR
Galantamine		Serious adverse events	IG3	5	140	14 (10.0)	286	31 (10.8)	NR
Galantamine		Withdrawals due to adverse events	IG1	5	273	27 (9.9)	286	20 (7.0)	NR
Galantamine		Withdrawals due to adverse events	IG2	5	279	19 (6.8)	286	20 (7.0)	NR
Galantamine		Withdrawals due to adverse events	IG3	5	140	9 (6.4)	286	20 (7.0)	NR
Galantamine	Wilcock, 2000[210] Fair-Good	Adverse events	IG1	6	220	182 (82.7)	215	165 (76.7)	NR
Galantamine		Adverse events	IG2	6	218	194 (89.0)	215	165 (76.7)	NR
Galantamine		Serious adverse events	IG1	6	220	28 (12.7)	215	26 (12.1)	NR
Galantamine		Serious adverse events	IG2	6	218	28 (12.8)	215	26 (12.1)	NR
Galantamine		Withdrawals due to adverse events	IG1	6	220	31 (14.1)	215	19 (8.8)	NR
Galantamine		Withdrawals due to adverse events	IG2	6	218	48 (22.0)	215	19 (8.8)	NR
Galantamine	Wilkinson, 2001[211] Fair-Good	Adverse events	IG1	3	56	33†	87	38†	NR
Galantamine		Adverse events	IG2	3	54	38†	87	38†	NR
Galantamine		Adverse events	IG3	3	88	49†	87	38†	NR
Galantamine	Wilkinson, 2001[211] Fair-Good	Serious adverse events	IG1	3	56	0 (0.0)	87	3 (3.4)	NR
Galantamine		Serious adverse events	IG2	3	54	5 (9.3)	87	3 (3.4)	NR

Appendix E Table 6. AChEIs and Memantine: Detailed Results for Harms, by Medication Type

Medication	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
Galantamine		Serious adverse events	IG3	3	88	6 (6.8)	87	3 (3.4)	NR
Galantamine		Withdrawals due to adverse events	IG1	3	56	10 (17.9)	87	8 (9.2)	NR
Galantamine		Withdrawals due to adverse events	IG2	3	54	24 (44.4)	87	8 (9.2)	NR
Galantamine		Withdrawals due to adverse events	IG3	3	88	19 (21.6)	87	8 (9.2)	NR
Rivastigmine	Agid, 1998[212] Fair-Good	Adverse events	IG1	3	133	133†	133	38†	NR
Rivastigmine		Adverse events	IG2	3	136	67†	133	38†	NR
Rivastigmine		Serious adverse events	IG1	3	133	8 (6.0)	133	2 (1.5)	NR
Rivastigmine		Serious adverse events	IG2	3	136	7 (5.1)	133	2 (1.5)	NR
Rivastigmine		Withdrawals due to adverse events	IG1	3	133	16 (12.0)	133	5 (3.8)	NR
Rivastigmine		Withdrawals due to adverse events	IG2	3	136	14 (10.3)	133	5 (3.8)	NR
Rivastigmine	Ballard, 2008[213] Fair	Serious adverse events	IG1	6	363	55 (15.2)	344	38 (11.0)	NR
Rivastigmine		Withdrawals due to adverse events	IG1	6	365	49 (13.4)	345	19 (5.5)	NR
Rivastigmine	Corey-Bloom, 1998[214] Fair-Good	Adverse events	IG1	6	231	NR	235	NR	NS
Rivastigmine		Adverse events	IG2	6	233	NR	235	NR	NS
Rivastigmine		Withdrawals due to adverse events	IG1	6	231	66 (28.6)	235	17 (7.2)	NR
Rivastigmine	Corey-Bloom, 1998[214] Fair-Good	Withdrawals due to adverse events	IG2	6	233	19 (8.2)	235	17 (7.2)	NR
Rivastigmine		Adverse events	IG1	6	227	208 (91.6)	222	169 (76.1)	NR

Appendix E Table 6. AChEIs and Memantine: Detailed Results for Harms, by Medication Type

Medication	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
Rivastigmine	Feldman, 2007[215] Fair	Adverse events	IG2	6	228	208 (91.2)	222	169 (76.1)	NR
Rivastigmine		Serious adverse events	IG1	6	227	40 (17.6)	222	33 (14.9)	NR
Rivastigmine		Serious adverse events	IG2	6	228	40 (17.5)	222	33 (14.9)	NR
Rivastigmine		Withdrawals due to adverse events	IG1	6	227	24 (10.6)	222	20 (9.0)	NR
Rivastigmine		Withdrawals due to adverse events	IG2	6	228	38 (16.7)	222	20 (9.0)	NR
Rivastigmine	McKeith, 2000[216] Fair-Good	Adverse events	IG1	5	59	54 (91.5)	61	46 (75.4)	NR
Rivastigmine		Serious adverse events	IG1	5	59	10 (16.9)	61	8 (13.1)	NR
Rivastigmine		Withdrawals due to adverse events	IG1	5	59	7 (11.9)	61	7 (11.5)	NR
Rivastigmine	Mok, 2007[217] Fair	Adverse events	IG1	6	20	12 (60.0)	20	10 (50.0)	NR
Rivastigmine		Withdrawals due to adverse events	IG1	6	20	6 (30.0)	20	3 (15.0)	NR
Rivastigmine	Rosler, 1999[218] Fair-Good	Adverse events	IG1	6	242	220 (90.9)	239	172 (72.0)	NR
Rivastigmine		Adverse events	IG2	6	242	172 (71.1)	239	172 (72.0)	NR
Rivastigmine		Serious adverse events	IG1	6	242	44 (18.2)	239	43 (18.0)	NR
Rivastigmine		Serious adverse events	IG2	6	242	44 (18.2)	239	43 (18.0)	NR
Rivastigmine		Withdrawals due to adverse events	IG1	6	242	55 (22.7)	239	16 (6.7)	NR
Rivastigmine		Withdrawals due to adverse events	IG2	6	242	18 (7.4)	239	16 (6.7)	NR
Rivastigmine	Winblad, 2007[219] Fair	Serious adverse events	IG1	6	294	21 (7.1)	302	27 (8.9)	NR
Rivastigmine		Serious adverse events	IG2	6	303	36 (11.9)	302	27 (8.9)	NR

Appendix E Table 6. AChEIs and Memantine: Detailed Results for Harms, by Medication Type

Medication	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
Rivastigmine		Serious adverse events	IG3	6	291	23 (7.9)	302	27 (8.9)	NR
Rivastigmine		Withdrawals due to adverse events	IG1	6	297	24 (8.1)	302	15 (5.0)	NR
Rivastigmine		Withdrawals due to adverse events	IG2	6	303	26 (8.6)	302	15 (5.0)	NR
Rivastigmine		Withdrawals due to adverse events	IG3	6	293	28 (9.6)	302	15 (5.0)	NR
Memantine	Bakchine, 2008[220] Good	Adverse events	IG1	6	318	178 (56.0)	152	80 (52.6)	NR
Memantine		Withdrawals due to adverse events	IG1	6	318	28 (8.8)	152	6 (3.9)	NR
Memantine	Choi, 2011*[221] Fair	Adverse events	IG1	4	88	47 (53.4)	83	42 (50.6)	NR, 0.71
Memantine		Serious adverse events	IG1	4	88	4 (4.5)	83	4 (4.8)	NR
Memantine		Withdrawals due to adverse events	IG1	4	88	6 (6.8)	83	4 (4.8)	NR, 0.82
Memantine	Dysken, 2014*[222] Good	Adverse events	IG1	48	155	97 (62.6)	152	89 (58.6)	NR
Memantine		Serious adverse events	IG1	48	155	84 (54.2)	152	95 (62.5)	NR
Memantine	Ferris, 2007[223] Fair	Adverse events	IG1	3	30	19 (63.3)	30	20 (66.7)	NR
Memantine		Serious adverse events	IG1	3	30	0 (0.0)	30	0 (0.0)	NR
Memantine	Herrmann, 2013*[224] Fair	Adverse events	IG1	6	182	138 (75.8)	187	136 (72.7)	NR
Memantine		Serious adverse events	IG1	6	182	18 (9.9)	187	11 (5.9)	NR
Memantine		Withdrawals due to adverse events	IG1	6	182	15 (8.2)	187	9 (4.8)	NR
Memantine	Orgogozo, 2002[225] Fair-Good	Adverse events	IG1	6	165	125 (75.8)	156	115 (73.7)	NR
Memantine		Serious adverse events	IG1	6	165	38 (23.0)	156	40 (25.6)	NR

Appendix E Table 6. AChEIs and Memantine: Detailed Results for Harms, by Medication Type

Medication	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
Memantine		Withdrawals due to adverse events	IG1	6	165	19 (11.5)	156	20 (12.8)	NR
Memantine	Peskind, 2006[226] Fair-Good	Adverse events	IG1	6	201	143 (71.1)	202	149 (73.8)	NR
Memantine		Serious adverse events	IG1	6	201	20 (10.0)	202	20 (9.9)	NR
Memantine		Withdrawals due to adverse events	IG1	6	201	19 (9.5)	202	10 (5.0)	NR, 0.09
Memantine	Peters, 2015*[227] Fair	Adverse events	IG1	12	112	89 (79.5)	114	80 (70.2)	NR, 0.108
Memantine		Serious adverse events	IG1	12	112	15 (13.4)	114	15 (13.2)	NR
Memantine	Porsteinsson, 2008[228] Good	Serious adverse events	IG1	6	217	27 (12.4)	216	30 (13.9)	NR
Memantine		Withdrawals due to adverse events	IG1	6	217	13 (6.0)	216	17 (7.9)	NR
Memantine	Saxton, 2012[229] Good	Adverse events	IG1	3	135	66 (48.9)	129	64 (49.6)	NR
Memantine		Serious adverse events	IG1	3	135	4 (3.0)	129	13 (10.1)	NR
Memantine		Withdrawals due to adverse events	IG1	3	136	3 (2.2)	129	4 (3.1)	NR
Memantine	Wilcock, 2002[230] Fair-Good	Adverse events	IG1	6	295	226 (76.6)	284	212 (74.6)	NR
Memantine		Serious adverse events	IG1	6	295	37 (12.5)	284	47 (16.5)	NR
Memantine		Withdrawals due to adverse events	IG1	6	295	27 (9.2)	284	20 (7.0)	NR
Memantine	Wilkinson, 2012[231] Fair	Adverse events	IG1	12	133	32 (24.1)	144	22 (15.3)	NR
Memantine		Serious adverse events	IG1	12	133	17 (12.8)	144	20 (13.9)	NR
Memantine	Wilkinson, 2012[231] Fair	Withdrawals due to adverse events	IG1	12	133	15 (11.3)	144	12 (8.3)	NR

* New study
† Number of events reported

Appendix E Table 6. AChEIs and Memantine: Detailed Results for Harms, by Medication Type

Abbreviations: CG = control group; FU = followup; IG = intervention group; Int arm = intervention arm; mo. = months; n (%) = number (percentage) of participants reporting events

Appendix F Table 1. Other Medications and Supplements: Detailed Results for Global Cognitive Function Outcomes, by Agent

Medication type	Intervention	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Antihypertensive	Discontinuation of antihypertensive	Moonen, 2015*[235] Fair	MCI	MMSE (0-30)	IG1	4	26‡ (NR)	180	NR	1.15 (0.85, 1.45)§	26‡ (NR)	176	NR	0.81 (0.51, 1.12)§	NR, 0.12
HMG-CoA reductase inhibitor	Atorvastatin	Feldman, 2010[236] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	3	22.3 (9.1)	296	NR	0.17‖ (0.27)¶	22.5 (9.9)	316	NR	0.35‖ (0.26)¶	LSM change (SE)=-0.18 (0.38), 0.63
HMG-CoA reductase inhibitor	Atorvastatin		Dem	ADAS-Cog 11 (0-70)	IG1	6	22.3 (9.1)	263	NR	0.36‖ (0.34)¶	22.5 (9.9)	308	NR	0.79‖ (0.32)¶	LSM change (SE)=-0.42 (0.47), 0.36
HMG-CoA reductase inhibitor	Atorvastatin		Dem	ADAS-Cog 11 (0-70)	IG1	11	22.3 (9.1)	236	NR	3.61‖ (0.45)¶	22.5 (9.9)	278	NR	4.12‖ (0.42)¶	LSM change (SE)=-0.51 (0.61), 0.41
HMG-CoA reductase inhibitor	Atorvastatin		Dem	ADAS-Cog 11 (0-70)	IG1	18	22.3 (9.1)	202	NR	5.98‖ (0.56)¶	22.5 (9.9)	235	NR	6.82‖ (0.52)¶	LSM change (SE)=-0.84 (0.76), 0.27
HMG-CoA reductase inhibitor	Atorvastatin		Dem	MMSE (0-30)	IG1	3	21.8 (3.2)	295	NR	0.11‖ (0.16)¶	21.9 (3.2)	316	NR	-0.07‖ (0.15)¶	LSM change (SE)=0.17 (0.22), 0.42
HMG-CoA reductase inhibitor	Atorvastatin		Dem	MMSE (0-30)	IG1	6	21.8 (3.2)	263	NR	-0.28‖ (0.17)¶	21.9 (3.2)	308	NR	-0.45‖ (0.16)¶	LSM change (SE)=0.16 (0.24), 0.49
HMG-CoA reductase inhibitor	Atorvastatin		Dem	MMSE (0-30)	IG1	11	21.8 (3.2)	236	NR	-0.96‖ (0.22)¶	21.9 (3.2)	278	NR	-1.35‖ (0.21)¶	LSM change (SE)=0.39 (0.31), 0.20
HMG-CoA reductase inhibitor	Atorvastatin		Dem	MMSE (0-30)	IG1	18	21.8 (3.2)	205	NR	-1.66‖ (0.26)¶	21.9 (3.2)	234	NR	-2.18‖ (0.24)¶	LSM change (SE)=0.52 (0.35), 0.14
HMG-CoA reductase inhibitor	Simvastatin	Sano, 2011[237] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	3	24.5 (9.7)	204	NR	1.89 (5.35)	23.9 (10.5)	202	NR	1.11 (5.32)	NS
HMG-CoA reductase inhibitor	Simvastatin	Sano, 2011[237] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	6	24.5 (9.7)	204	NR	2.51 (5.61)	23.9 (10.5)	202	NR	2.32 (5.9)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	ADAS-Cog 11 (0-70)	IG1	12	24.5 (9.7)	204	NR	5.79 (7.76)	23.9 (10.5)	202	NR	5.36 (6.95)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	ADAS-Cog 11 (0-70)	IG1	18	24.5 (9.7)	204	NR	9.51 (9.48)	23.9 (10.5)	202	NR	8.18 (8.7)	NS

Appendix F Table 1. Other Medications and Supplements: Detailed Results for Global Cognitive Function Outcomes, by Agent

Medication type	Intervention	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
HMG-CoA reductase inhibitor	Simvastatin		Dem	MMSE (0-30)	IG1	3	20.0 (4.5)	204	NR	-0.52 (2.74)	20.7 (4.9)	202	NR	-0.1 (3.1)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	MMSE (0-30)	IG1	6	20.0 (4.5)	204	NR	-0.72 (3.26)	20.7 (4.9)	202	NR	-0.89 (3.23)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	MMSE (0-30)	IG1	12	20.0 (4.5)	204	NR	-2.47 (3.8)	20.7 (4.9)	202	NR	-2.28 (4.08)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	MMSE (0-30)	IG1	18	20.0 (4.5)	204	NR	-4.23 (4.77)	20.7 (4.9)	202	NR	-3.75 (4.38)	NS
HMG-CoA reductase inhibitor	Simvastatin	Simons, 2002[238] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	6	29.4 (10.4)	20	NR	4.1 (6.5)	33.2 (11.3)	17	NR	3.4 (7.0)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	MMSE (0-30)	IG1	6	17.8 (5.0)	20	17.2 (4.8)	NR	17.1 (4.9)	17	14.4 (5.6)	NR	NR, <0.02
HMG-CoA reductase inhibitor	Atorvastatin	Sparks, 2005[239] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	3	20.6 (1.73)¶	32	20.5 (NR)	NR	19.9 (1.73)¶	31	20.7 (NR)	NR	NS
HMG-CoA reductase inhibitor	Atorvastatin		Dem	ADAS-Cog 11 (0-70)	IG1	6	20.6 (1.73)¶	32	18.8 (1.4)¶	NR	19.9 (1.73)¶	31	22.1 (1.9)	NR	NR, 0.003
HMG-CoA reductase inhibitor	Atorvastatin		Dem	ADAS-Cog 11 (0-70)	IG1	8	20.6 (1.73)¶	32	20.8 (1.5)¶	NR	19.9 (1.73)¶	31	22.8 (1.5)¶	NR	NR, 0.18
HMG-CoA reductase inhibitor	Atorvastatin		Dem	ADAS-Cog 11 (0-70)	IG1	12	20.6 (1.73)¶	32	20.3 (1.7)¶	NR	19.9 (1.73)¶	31	23.6 (2.0)¶	NR	NR, 0.055
HMG-CoA reductase inhibitor	Atorvastatin	Sparks, 2005[239] Fair	Dem	MMSE (0-30)	IG1	3	21.09 (0.61)¶	32	20.2 (NR)	NR	20.52 (0.76)¶	31	20.5 (NR)	NR	NS
HMG-CoA reductase inhibitor	Atorvastatin		Dem	MMSE (0-30)	IG1	6	21.09 (0.61)¶	32	21.2 (0.8)¶	NR	20.52 (0.76)¶	31	19.4 (1.0)¶	NR	NR, 0.46
HMG-CoA reductase inhibitor	Atorvastatin		Dem	MMSE (0-30)	IG1	8	21.09 (0.61)¶	32	20.7 (0.7)¶	NR	20.52 (0.76)¶	31	18.1 (1.1)¶	NR	NR, 0.41

Appendix F Table 1. Other Medications and Supplements: Detailed Results for Global Cognitive Function Outcomes, by Agent

Medication type	Intervention	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
HMG-CoA reductase inhibitor	Atorvastatin		Dem	MMSE (0-30)	IG1	12	21.09 (0.61)¶	32	20.3 (0.9)¶	NR	20.52 (0.76)¶	31	18.1 (1.1)¶	NR	NR, 0.25
NSAID	Naproxen	Aisen, 2003[240] Good	Dem	ADAS-Cog 11 (0-70)	IG1	12	24.4 (10.2)	118	30.2 (13.9)	5.8 (8.0)	24.2 (9.6)	111	29.9 (13.7)	5.7 (8.2)	MDC (SE) (95% CI)=-0.1 (1.07) (-2.24, 2.04), 0.96
NSAID	Indomethacin	de Jong, 2008[241] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	6	20.2 (8.3)	20	NR	4.8 (5.8)	19.7 (8.8)	23	NR	3.9 (4.5)	MDC (95% CI)=0.9 (-2.2, 4.1), NR
NSAID	Indomethacin		Dem	ADAS-Cog 11 (0-70)	IG1	12	20.2 (8.3)	19	NR	7.8 (7.6)	19.7 (8.8)	19	NR	9.3 (10.0)	MDC (95% CI)=-1.5 (-7.5, 4.5), NR
NSAID	Indomethacin		Dem	MMSE (0-30)	IG1	6	19.1 (4.1)	20	NR	-2.3 (3.2)	20.2 (3.9)	23	NR	-2.4 (3.6)	MDC (95% CI)=-0.1 (-2.1, 1.9), NR
NSAID	Indomethacin		Dem	MMSE (0-30)	IG1	12	19.1 (4.1)	19	NR	-3.4 (4.3)	20.2 (3.9)	19	NR	-5.4 (5.5)	MDC (95% CI)=-1.6 (-4.8, 1.6), NR
NSAID	Ibuprofen	Pasqualetti, 2009[242] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	12	26.8 (10.6)	66	NR	-3.0 (1.3)¶	25.6 (10.7)	66	NR	-3.1 (1.3)¶	MDC (95% CI)=0.1 (-2.7, 2.9), 0.951
NSAID	Ibuprofen		Dem	MMSE (0-30)	IG1	12	19.7 (3.0)	66	NR	2.1 (0.5)¶	20.3 (3.8)	66	NR	2.7 (0.5)¶	MDC (95% CI)=-0.6 (-1.8, 0.5), 0.288
NSAID	Celecoxib	Soininen, 2007[243] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	3	24.8 (10.7)	263	NR	0.77‖ (NR)	24.6 (10.1)	124	NR	0.69‖ (NR)	NR, 0.897
NSAID	Celecoxib		Dem	ADAS-Cog 11 (0-70)	IG1	6	24.8 (10.7)	274	NR	1.64‖ (NR)	24.6 (10.1)	135	NR	2.15‖ (NR)	NR, 0.461
NSAID	Celecoxib	Soininen, 2007[243] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	12	24.8 (10.7)	278	NR	4.39‖ (NR)	24.6 (10.1)	135	NR	5.00‖ (NR)	NR, 0.541
NSAID	Celecoxib		Dem	ADAS-Cog 11 (D)	IG1	12	NA	278	158 (56.8)#	NR	NA	135	85 (63.0)#	NR	NS
NSAID	Celecoxib		Dem	MMSE (0-30)	IG1	12	19.8 (4.2)	255	NR	-2.3 (NR)	19.4 (3.9)	128	NR	-2.0 (NR)	NR, 0.244

Appendix F Table 1. Other Medications and Supplements: Detailed Results for Global Cognitive Function Outcomes, by Agent

Medication type	Intervention	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Gonadal steroid	Estrogen	Henderson, 2000[245] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	4	25.1 (2.2)¶	17	26.9 (2.6)¶	1.8 (1.2)¶	26.8 (2.8)¶	17	27.3 (2.5)¶	0.5 (1.7)¶	MDC =1.3, >0.1
Gonadal steroid	Estrogen		Dem	ADAS-Cog 11 (D)	IG1	4	NA	17	2 (11.8)**	NR	NA	17	5 (29.4)**	NR	NR
Gonadal steroid	Estrogen	Henderson, 2015*[244] Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	24.3 (11.0)	21	NR	-1.5 (NR)	25.8 (12.0)	21	NR	2.3 (NR)	ES (95% CI)=-0.33 (-0.66, 0.003), 0.048
Gonadal steroid	Estrogen		Dem	ADAS-Cog 11 (0-70)	IG1	6	24.3 (11.0)	21	NR	-0.7 (NR)	25.8 (12.0)	21	NR	1.8 (NR)	ES (95% CI)=-0.22 (-0.54, 0.10), 0.18
Gonadal steroid	Estrogen		Dem	ADAS-Cog 11 (0-70)	IG1	9	24.3 (11.0)	21	NR	-1.1 (NR)	25.8 (12.0)	21	NR	1.3 (NR)	ES (95% CI)=-0.21 (-0.52, 1.10), 0.17
Gonadal steroid	Estrogen		Dem	ADAS-Cog 11 (0-70)	IG1	12	24.3 (11.0)	21	NR	3.2 (NR)	25.8 (12.0)	21	NR	3.5 (NR)	ES (95% CI)=-0.03 (-0.44, 0.39), 0.89
Gonadal steroid	Estrogen		Dem	MMSE (0-30)	IG1	6	21.2 (4.9)	21	NR	-0.8 (NR)	19.4 (6.2)	21	NR	-0.6 (NR)	ES (95% CI)=-0.05 (-0.44, 0.35), NR
Gonadal steroid	Estrogen		Dem	MMSE (0-30)	IG1	12	21.2 (4.9)	21	NR	-2.5 (NR)	19.4 (6.2)	21	NR	-1.6 (NR)	ES (95% CI)=-0.17 (-0.65, 0.31), NR
Gonadal steroid	Testosterone	Lu, 2006[246] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	6	25.0 (13.2)	5	27.4 (8.4)	2.4 (5.0)	25.2 (8.9)	6	28.3 (10.3)	3.2 (7.3)	NR, 0.82
Gonadal steroid	Estrogen	Mulnard, 2000[247] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	12	NR	42	NR	6.3 (8.7)	NR	39	NR	3.6 (4.7)	NR, 0.09
Gonadal steroid	Estrogen		Dem	ADAS-Cog 11 (0-70)	IG2	12	NR	39	NR	4.8 (5.4)	NR	39	NR	3.6 (4.7)	NR, 0.32
Gonadal steroid	Estrogen		Dem	MMSE (0-30)	IG1	12	20.2 (4.7)	42	NR	-2.7 (3.5)	21.1 (3.3)	39	NR	-3.1 (4.1)	NR, 0.48

Appendix F Table 1. Other Medications and Supplements: Detailed Results for Global Cognitive Function Outcomes, by Agent

Medication type	Intervention	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Gonadal steroid	Estrogen		Dem	MMSE (0-30)	IG2	12	20.8 (4.2)	39	NR	-2.7 (3.9)	21.1 (3.3)	39	NR	-3.1 (4.1)	NR, 0.64
Gonadal steroid	Estrogen plus progestin	Valen-Sendstad, 2010[248] Fair	Dem	MMSE (0-30)	IG1	12	22.0 (4.3)	29	19.9 (4.7)	NR	21.8 (3.9)	26	19.8 (4.9)	NR	MDC (SD)=-0.1 (3.1), 0.90
Gonadal steroid	Estrogen	Wang, 2000[249] Fair	Dem	MMSE (0-30)	IG1	3	16.1 (4.3)	25	NR	0.2 (3.3)	16.2 (4.2)	25	NR	0.2 (2.5)	NR, 0.975
Dietary supplement	B vitamins (including folic acid)	Aisen, 2008[250] Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	22.43 (9.0)	234	NR	1.58 (5.61)	22.63 (8.6)	161	NR	1.51 (4.68)	NR
Dietary supplement	B vitamins (including folic acid)		Dem	ADAS-Cog 11 (0-70)	IG1	6	22.43 (9.0)	232	NR	2.44 (6.04)	22.63 (8.6)	156	NR	1.72 (4.74)	NR
Dietary supplement	B vitamins (including folic acid)		Dem	ADAS-Cog 11 (0-70)	IG1	12	22.43 (9.0)	216	NR	4.42 (6.61)	22.63 (8.6)	143	NR	4.46 (6.32)	NR
Dietary supplement	B vitamins (including folic acid)		Dem	ADAS-Cog 11 (0-70)	IG1	18	22.43 (9.0)	197	NR	7.38 (9.72)	22.63 (8.6)	136	NR	6.54 (8.17)	NR
Dietary supplement	B vitamins (including folic acid)		Dem	MMSE (0-30)	IG1	3	20.98 (3.4)	235	NR	-0.17 (3.02)	20.91 (3.7)	164	NR	-0.67 (2.89)	NR
Dietary supplement	B vitamins (including folic acid)		Dem	MMSE (0-30)	IG1	6	20.98 (3.4)	231	NR	-0.44 (3.19)	20.91 (3.7)	160	NR	-1.13 (3.13)	NR
Dietary supplement	B vitamins (including folic acid)		Dem	MMSE (0-30)	IG1	12	20.98 (3.4)	215	NR	-1.64 (3.84)	20.91 (3.7)	147	NR	-1.8 (3.56)	NR
Dietary supplement	B vitamins (including folic acid)	Aisen, 2008[250] Good	Dem	MMSE (0-30)	IG1	18	20.98 (3.4)	206	NR	-2.65 (4.56)	20.91 (3.7)	140	NR	-3.08 (4.46)	NR
Dietary supplement	B vitamins (including folic acid)	Connelly, 2008[251] Fair	Dem	MMSE (0-30)	IG1	6	23.48 (4.1)	23	NR	0.09 (3.3)	23.5 (2.75)	18	NR	0.22 (2.67)	NR
Dietary supplement	Vitamin E	Dysken, 2014*[222] Good	Dem	ADAS-Cog 11 (0-70)	IG2	6	18.5 (8.8)	126	NR	1.37‖ (0.13, 2.63)§	19.1 (8.4)	128	NR	3.04‖ (1.81, 4.28)§	NR

Appendix F Table 1. Other Medications and Supplements: Detailed Results for Global Cognitive Function Outcomes, by Agent

Medication type	Intervention	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Dietary supplement	Vitamin E		Dem	ADAS-Cog 11 (0-70)	IG2	12	18.5 (8.8)	114	NR	2.38‖ (0.98, 3.82)§	19.1 (8.4)	106	NR	4.24‖ (2.81, 5.70)§	NR
Dietary supplement	Vitamin E		Dem	ADAS-Cog 11 (0-70)	IG2	18	18.5 (8.8)	89	NR	4.33‖ (2.57, 6.12)§	19.1 (8.4)	88	NR	6.04‖ (4.25, 7.86)§	NR
Dietary supplement	Vitamin E		Dem	ADAS-Cog 11 (0-70)	IG2	24	18.5 (8.8)	82	NR	4.32‖ (2.16, 6.47)§	19.1 (8.4)	69	NR	6.70‖ (4.43, 8.97)§	NR
Dietary supplement	Vitamin E		Dem	ADAS-Cog 11 (0-70)	IG2	30	18.5 (8.8)	56	NR	7.86‖ (5.30, 10.42)§	19.1 (8.4)	48	NR	8.9‖ (6.20, 11.62)§	NR
Dietary supplement	Vitamin E		Dem	ADAS-Cog 11 (0-70)	IG2	36	18.5 (8.8)	42	NR	8.99‖ (6.02, 12.00)§	19.1 (8.4)	35	NR	10.76‖ (7.58, 13.96)§	NR
Dietary supplement	Vitamin E		Dem	ADAS-Cog 11 (0-70)	IG2	42	18.5 (8.8)	27	NR	10.34‖ (7.22, 13.49)§	19.1 (8.4)	25	NR	10.60‖ (7.30, 13.92)§	NR
Dietary supplement	Vitamin E		Dem	ADAS-Cog 11 (0-70)	IG2	48	18.5 (8.8)	135	NR	5.97‖ (0.70)¶	19.1 (8.4)	137	NR	7.78‖ (0.70)¶	MDC (95% CI)=-1.80 (-3.28, -0.33), 0.10
Dietary supplement	Vitamin E		Dem	MMSE (0-30)	IG2	6	21.3 (3.3)	126	NR	-0.34‖ (-0.90, 0.22)§	20.8 (3.8)	128	NR	-0.34‖ (-0.91, 0.23)§	NR
Dietary supplement	Vitamin E		Dem	MMSE (0-30)	IG2	12	21.3 (3.3)	115	NR	-0.96‖ (-1.62, -0.27)§	20.8 (3.8)	106	NR	-1.39‖ (-2.08, -0.69)§	NR
Dietary supplement	Vitamin E		Dem	MMSE (0-30)	IG2	18	21.3 (3.3)	89	NR	-2.00‖ (-2.86, -1.12)§	20.8 (3.8)	88	NR	-2.21‖ (-3.09, -1.31)§	NR
Dietary supplement	Vitamin E		Dem	MMSE (0-30)	IG2	24	21.3 (3.3)	83	NR	-2.63‖ (-3.65, -1.58)§	20.8 (3.8)	70	NR	-2.90‖ (-3.99, -1.80)§	NR
Dietary supplement	Vitamin E	Dysken, 2014*[222] Good	Dem	MMSE (0-30)	IG2	30	21.3 (3.3)	56	NR	-3.67‖ (-4.86, -2.47)§	20.8 (3.8)	47	NR	-3.27‖ (-4.53, -2.01)§	NR
Dietary supplement	Vitamin E		Dem	MMSE (0-30)	IG2	36	21.3 (3.3)	43	NR	-4.98‖ (-6.44, -3.51)§	20.8 (3.8)	36	NR	-3.88‖ (-5.43, -2.31)§	NR
Dietary supplement	Vitamin E		Dem	MMSE (0-30)	IG2	42	21.3 (3.3)	27	NR	-4.85‖ (-6.41, -3.28)§	20.8 (3.8)	26	NR	-4.68‖ (-6.29, -3.05)§	NR

Appendix F Table 1. Other Medications and Supplements: Detailed Results for Global Cognitive Function Outcomes, by Agent

Medication type	Intervention	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Dietary supplement	Vitamin E		Dem	MMSE (0-30)	IG2	48	21.3 (3.3)	136	NR	-2.97‖ (0.33)¶	20.8 (3.8)	137	NR	-3.16‖ (0.33)¶	MDC (95% CI)=0.19 (-0.54, 0.92), 0.84
Dietary supplement	Omega-3 fatty acids	Freund-Levi, 2006[253] Fair	Dem	ADAS-Cog 13 (0-85)	IG1	6	25.7 (NR)	91	27.7 (NR)	NR	27.2 (NR)	87	28.3 (NR)	NR	NR
Dietary supplement	Omega-3 fatty acids		Dem	MMSE (0-30)	IG1	6	23.6	91	22.8	NR	23.2	87	22.4	NR	NR
Dietary supplement	B vitamins (including folic acid)	Kwok, 2011[254] Fair	Dem	MDRS (0-144)	IG1	24	104.2 (13.0)	59	NR	-6†† (-14, -2)	103.7 (10.6)	53	NR	-6†† (-15, 0)	NR, 0.841
Dietary supplement	B vitamins (including folic acid)		Dem	MMSE (0-30)	IG1	24	16.5 (4.9)	59	NR	-2†† (-5, 0)	16.6 (4.6)	53	NR	-2†† (-5, 0)	NR, 0.998
Dietary supplement	Vitamin E	Petersen, 2005[194] Fair	MCI	ADAS-Cog 11 (0-70)	IG2	6	11.48 (4.4)	NR	NR	-0.16 (4.19)	11.03 (4.2)	NR	NR	-0.13 (3.34)	NR
Dietary supplement	Vitamin E		MCI	ADAS-Cog 11 (0-70)	IG2	12	11.48 (4.4)	NR	NR	0.91 (4.21)	11.03 (4.2)	NR	NR	0.61 (4.10)	NR
Dietary supplement	Vitamin E		MCI	ADAS-Cog 11 (0-70)	IG2	18	11.48 (4.4)	NR	NR	1.19 (4.32)	11.03 (4.2)	NR	NR	1.29 (4.71)	NR
Dietary supplement	Vitamin E		MCI	ADAS-Cog 11 (0-70)	IG2	24	11.48 (4.4)	NR	NR	1.93 (5.13)	11.03 (4.2)	NR	NR	1.49 (5.07)	NR
Dietary supplement	Vitamin E		MCI	ADAS-Cog 11 (0-70)	IG2	30	11.48 (4.4)	NR	NR	3.01 (5.57)	11.03 (4.2)	NR	NR	2.98 (5.62)	NR
Dietary supplement	Vitamin E		MCI	ADAS-Cog 11 (0-70)	IG2	36	11.48 (4.4)	185	NR	4.59 (6.54)	11.03 (4.2)	193	NR	3.74 (6.97)	NR
Dietary supplement	Vitamin E		MCI	ADAS-Cog 13 (0-85)	IG2	6	18.04 (6.0)	NR	NR	-0.47 (5.06)	17.40 (6.0)	NR	NR	-0.09 (4.38)	NR
Dietary supplement	Vitamin E		MCI	ADAS-Cog 13 (0-85)	IG2	12	18.04 (6.0)	NR	NR	0.27 (5.20)	17.40 (6.0)	NR	NR	0.60 (4.96)	NR
Dietary supplement	Vitamin E	Petersen, 2005[194] Fair	MCI	ADAS-Cog 13 (0-85)	IG2	18	18.04 (6.0)	NR	NR	0.49 (5.42)	17.40 (6.0)	NR	NR	0.99 (6.07)	NR
Dietary supplement	Vitamin E		MCI	ADAS-Cog 13 (0-85)	IG2	24	18.04 (6.0)	NR	NR	1.15 (6.37)	17.40 (6.0)	NR	NR	1.02 (6.27)	NR
Dietary supplement	Vitamin E		MCI	ADAS-Cog 13 (0-85)	IG2	30	18.04 (6.0)	NR	NR	2.48 (6.68)	17.40 (6.0)	NR	NR	2.65 (7.02)	NR
Dietary supplement	Vitamin E		MCI	ADAS-Cog 13 (0-85)	IG2	36	18.04 (6.0)	185	NR	3.98 (7.56)	17.40 (6.0)	193	NR	3.72 (8.54)	NR

Appendix F Table 1. Other Medications and Supplements: Detailed Results for Global Cognitive Function Outcomes, by Agent

Medication type	Intervention	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Dietary supplement	Vitamin E		MCI	MMSE (0-30)	IG2	6	27.20 (1.9)	NR	NR	-0.53 (2.28)	27.35 (1.8)	NR	NR	-0.36 (2.02)	NR
Dietary supplement	Vitamin E		MCI	MMSE (0-30)	IG2	12	27.20 (1.9)	NR	NR	-0.54 (2.28)	27.35 (1.8)	NR	NR	-0.80 (2.34)	NR
Dietary supplement	Vitamin E		MCI	MMSE (0-30)	IG2	18	27.20 (1.9)	NR	NR	-0.96 (2.61)	27.35 (1.8)	NR	NR	-1.02 (2.61)	NR
Dietary supplement	Vitamin E		MCI	MMSE (0-30)	IG2	24	27.20 (1.9)	NR	NR	-1.21 (2.78)	27.35 (1.8)	NR	NR	-1.49 (2.90)	NR
Dietary supplement	Vitamin E		MCI	MMSE (0-30)	IG2	30	27.20 (1.9)	NR	NR	-1.75 (3.09)	27.35 (1.8)	NR	NR	-1.77 (3.24)	NR
Dietary supplement	Vitamin E		MCI	MMSE (0-30)	IG2	36	27.20 (1.9)	185	NR	-2.20 (3.64)	27.35 (1.8)	193	NR	-2.75 (4.04)	NR
Dietary supplement	Omega-3 fatty acids	Quinn, 2010[256] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	6	23.77 (8.9)	215	NR	2.7 (1.8, 3.3)§	23.96 (9.2)	147	NR	3.1 (2.0, 3.9)§	NR
Dietary supplement	Omega-3 fatty acids		Dem	ADAS-Cog 11 (0-70)	IG1	12	23.77 (8.9)	190	NR	4.0 (3.0, 5.0)§	23.96 (9.2)	139	NR	5.5 (4.4, 6.7)§	NR
Dietary supplement	Omega-3 fatty acids		Dem	ADAS-Cog 11 (0-70)	IG1	18	23.77 (8.9)	173	NR	7.98 (6.51, 9.45)§	23.96 (9.2)	127	NR	8.27 (6.72, 9.82)§	MDC (95% CI)=NR (NR, NR), 0.41
Dietary supplement	Omega-3 fatty acids		Dem	MMSE (0-30)	IG1	18	20.9 (3.6)	173	NR	-3.70 (-4.44, -2.96)§	20.3 (3.7)	127	NR	-4.04 (-4.85, -3.23)§	MDC (95% CI)=NR (NR, NR), 0.88
Dietary supplement	Vitamin E	Sano, 1997[257] Good	Dem	ADAS-Cog 11 (0-70)	IG1	24	NR	85	NR	8.3 (NR)	NR	84	NR	6.7 (NR)	NR
Dietary supplement	Vitamin E		Dem	MMSE (0-30)	IG1	24	11.3 (5.7)	85	NR	-4.6 (NR)	13.3 (4.9)	84	NR	-4.6 (NR)	NR
Dietary supplement	Omega-3 fatty acids	Shinto, 2014*[258] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	12	31.8 (9.4)¶	11	NR	4.4 (2.2)¶	32.2 (9.5)¶	11	NR	3.2 (2.1)¶	NR, 0.86
Dietary supplement	Omega-3 fatty acids		Dem	ADAS-Cog 11 (0-70)	IG2	12	29.0 (7.1)¶	12	NR	2.8 (2.0)¶	32.2 (9.5)¶	11	NR	3.2 (2.1)¶	NR, 0.98
Dietary supplement	Omega-3 fatty acids	Shinto, 2014*[258] Fair	Dem	MMSE (0-30)	IG1	6	20.7 (2.7)¶	11	NR	-1.63 (0.97)¶	22.2 (3.1)¶	11	NR	-1.59 (1.09)¶	NR, NR
Dietary supplement	Omega-3 fatty acids		Dem	MMSE (0-30)	IG1	12	20.7 (2.7)¶	11	NR	-4.3 (1.3)¶	22.2 (3.1)¶	11	NR	-4.6 (1.4)¶	NR, 0.80
Dietary supplement	Omega-3 fatty acids		Dem	MMSE (0-30)	IG2	6	22.5 (3.0)¶	12	NR	0.83 (0.80)¶	22.2 (3.1)¶	11	NR	-1.59 (1.09)¶	NR
Dietary supplement	Omega-3 fatty acids		Dem	MMSE (0-30)	IG2	12	22.5 (3.0)¶	12	NR	-1.0 (0.7)¶	22.2 (3.1)¶	11	NR	-4.6 (1.4)¶	NR, <0.01

Appendix F Table 1. Other Medications and Supplements: Detailed Results for Global Cognitive Function Outcomes, by Agent

Medication type	Intervention	Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Dietary supplement	Multivitamin	Sun, 2007[260] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	6	24.0 (12.3)	45	NR	0.67 (-2.33, 3.69)§	21.2 (10.5)	44	NR	-0.9 (-2.77, 0.85)§	NR, 0.34
Dietary supplement	Multivitamin	Sun, 2007[260] Fair	Dem	MMSE (0-30)	IG1	6	18.7 (4.6)	45	NR	0.15 (-1.06, 1.35)§	18.6 (5.3)	44	NR	0.41 (-1.12, 1.93)§	NR, 0.79
Dietary supplement	Omega-3 fatty acids	Yurko-Mauro, 2010[261] Good	MCI	MMSE (0-30)	IG1	6	28.3 (1.3)	241	28.0 (1.9)	-0.4 (0.12)¶	28.2 (1.3)	242	27.9 (1.9)	-0.3 (0.11)¶	MDC (SE)=0 (0.15), 0.866

* New study
† Higher scores indicate better outcomes for all instruments except for ADAS-Cog 11 and ADAS-Cog 13 where lower scores indicate better outcomes
‡ Median
§ 95% CI
‖ Least squares mean change
¶ Standard error
# Number (%) of participants who demonstrated deterioration (≥4 point increase) on ADAS-Cog 11
** Number (%) of participants who improved by ≥4 points (decreasing) on ADAS-Cog 11
†† Median change (IQR)

Abbreviations: ADAS-Cog 11 = Alzheimer's Disease Assessment Scale-cognitive subscale; 11-item; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-cognitive subscale; 13-item; BL = baseline; CG = control group; CI = confidence interval; D = results are dichotomized; Dem = dementia; ES = effect size; FU = followup; HMG-CoA = β-Hydroxy β-methylglutaryl-CoA; IG = intervention group; Int arm = intervention arm; LSM = least squares mean; MCI = mild cognitive impairment; MDC = mean difference in change; MMSE = Mini-Mental State Examination; mo. = months; Pop cat = population category; NR = not reported; NS = Not statistically significant; NSAID = Nonsteroidal Anti-inflammatory Drug; SD = standard deviation; SE = standard error

Appendix F Table 2. Other Medications and Supplements: Detailed Results for Global Function Outcomes, by Agent

Medication type	Medication	Author, year Quality	Pop cat	Instrument (range)*	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
HMG-CoA reductase inhibitor	Atorvastatin	Feldman, 2010[236] Fair	Dem	CDR-SB (0-18)	IG1	11	5.7 (2.4)	272	NR	1.34§ (0.14)‡	5.9 (2.5)	296	NR	1.35§ (0.13)‡	LSM change (SE)=-0.01 (0.19), 0.96
HMG-CoA reductase inhibitor	Atorvastatin		Dem	CDR-SB (0-18)	IG1	18	5.7 (2.4)	208	NR	1.98§ (0.18)‡	5.9 (2.5)	238	NR	2.11§ (0.17)‡	LSM change (SE)=-0.12 (0.25), 0.63
HMG-CoA reductase inhibitor	Atorvastatin		Dem	CIBIC+ (1-7)	IG1	3	NR	293	4.2† (0.04)‡	NR	NR	310	4.2† (0.04)‡	NR	MD (SE)=0.010 (0.058), 0.8654
HMG-CoA reductase inhibitor	Atorvastatin		Dem	CIBIC+ (1-7)	IG1	6	NR	258	4.3† (0.06)‡	NR	NR	306	4.4† (0.03)‡	NR	MD (SE)=0.032 (0.073), 0.6578
HMG-CoA reductase inhibitor	Atorvastatin		Dem	CIBIC+ (1-7)	IG1	9	NR	244	4.6† (0.07)‡	NR	NR	283	4.6† (0.06)‡	NR	MD (SE)=-0.021 (0.081), 0.7937
HMG-CoA reductase inhibitor	Atorvastatin		Dem	CIBIC+ (1-7)	IG1	12	NR	233	4.8† (0.07)‡	NR	NR	272	4.8† (0.07)‡	NR	MD (SE)=-0.034 (0.083), 0.6817
HMG-CoA reductase inhibitor	Atorvastatin		Dem	CIBIC+ (1-7)	IG1	15	NR	222	4.9† (0.06)‡	NR	NR	264	5.0† (0.07)‡	NR	MD (SE)=0.019 (0.090), 0.8363
HMG-CoA reductase inhibitor	Atorvastatin		Dem	CIBIC+ (1-7)	IG1	18	NR	297	4.9† (0.06)‡	NR	NR	317	5.1† (0.07)‡	NR	MD (SE)=0.160 (0.086), 0.628
HMG-CoA reductase inhibitor	Atorvastatin	Sparks, 2005[239] Fair	Dem	CIBIC+ (1-7)	IG1	3	NR	32	NR	-0.36 (NR)	NR	31	NR	-0.40 (NR)	NS
HMG-CoA reductase inhibitor	Atorvastatin		Dem	CIBIC+ (1-7)	IG1	6	NR	29	NR	-0.53 (NR)	NR	27	NR	-0.68 (NR)	NR, 0.62
HMG-CoA reductase inhibitor	Atorvastatin		Dem	CIBIC+ (1-7)	IG1	8	NR	26	NR	-0.57 (0.16)‡	NR	22	NR	-0.90 (0.14)‡	NR, 0.058
HMG-CoA reductase inhibitor	Atorvastatin		Dem	CIBIC+ (1-7)	IG1	12	NR	25	NR	-0.73 (0.20)‡	NR	21	NR	-1.04 (0.15)‡	NR, 0.07
NSAID	Naproxen	Aisen, 2003[240] Good	Dem	CDR-SB (0-18)	IG1	12	6.0 (2.9)	118	8.3 (4.0)	2.3 (2.3)	5.5 (2.5)	111	7.7 (3.9)	2.2 (2.3)	NR, 0.89

Appendix F Table 2. Other Medications and Supplements: Detailed Results for Global Function Outcomes, by Agent

Medication type	Medication	Author, year Quality	Pop cat	Instrument (range)*	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
NSAID	Indomethacin	de Jong, 2008[241] Fair	Dem	CIBIC+ (1-7)	IG1	6	NR	20	5.1 (0.8)	NR	NR	23	5.3 (0.7)	NR	MD (95% CI)=-0.2 (-0.6, 0.2), NS
NSAID	Indomethacin		Dem	CIBIC+ (1-7)	IG1	12	NR	19	5.6 (0.8)	NR	NR	19	5.7 (0.7)	NR	MD (95% CI)=-0.1 (-0.5, 0.3), NS
NSAID	Ibuprofen	Pasqualetti, 2009[242] Fair	Dem	CDR-SB (0-18)	IG1	12	4.5 (2.0)	66	NR	-1.7 (0.3)‡	4.4 (2.1)	66	NR	-1.3 (0.4)‡	MDC (95% CI)=-0.4 (-1.2, 0.4), 0.324
NSAID	Ibuprofen		Dem	CIBIC+ (1-7)	IG1	12	NR	66	4.0 (0.2)‡	NR	NR	66	3.9 (0.2)‡	NR	MD (95% CI)=0.1 (-0.4, 0.5), 0.741
NSAID	Celecoxib	Soininen, 2007[243] Fair	Dem	CIBIC+ (1-7)	IG1	3	NR	261	4.25† (NR)	NR	NR	122	4.30† (NR)	NR	NR, 0.571
NSAID	Celecoxib		Dem	CIBIC+ (1-7)	IG1	6	NR	276	4.51† (NR)	NR	NR	135	4.40† (NR)	NR	NR, 0.277
NSAID	Celecoxib		Dem	CIBIC+ (1-7)	IG1	12	NR	279	4.92† (NR)	NR	NR	135	4.83† (NR)	NR	NR, 0.446
NSAID	Celecoxib		Dem	CIBIC+ (D)	IG1	12	NA	278	201 (72.0)‖	NR	NA	135	99 (73.3)‖	NR	NS
Gonadal steroid	Estrogen	Henderson, 2000[245] Fair	Dem	CIBIC+ (1-7)	IG1	4	NR	18	4.2 (0.2)‡	NR	NR	18	4.2 (0.1)‡	NR	MD=-0.1, >0.1
Gonadal steroid	Estrogen		Dem	CIBIC+ (D)	IG1	4	NA	18	13 (72.2)¶	NR	NA	18	14 (77.8)¶	NR	NR
Gonadal steroid	Estrogen	Henderson, 2015[244#] Good	Dem	CDR (0-3)	IG1	6	1.0 (0.5)	21	NR	0.2 (NR)	1.2 (0.6)	21	NR	0.2 (NR)	ES (95% CI)=0.08 (-0.57, 0.74), NS
Gonadal steroid	Estrogen		Dem	CDR (0-3)	IG1	12	1.0 (0.5)	21	NR	0.5 (NR)	1.2 (0.6)	21	NR	0.3 (NR)	ES (95% CI)=0.30 (-0.56, 1.16), NS
Gonadal steroid	Estrogen		Dem	CDR-SB (0-18)	IG1	6	5.5 (3.0)	21	NR	0.8 (NR)	6.8 (3.1)	21	NR	1.0 (NR)	ES (95% CI)=-0.07 (-0.58, 0.44), NS
Gonadal steroid	Estrogen		Dem	CDR-SB (0-18)	IG1	12	5.5 (3.0)	21	NR	2.6 (NR)	6.8 (3.1)	21	NR	2.0 (NR)	ES (95% CI)=0.18 (-0.39, 0.75), NS
Gonadal steroid	Testosterone	Lu, 2006[246] Fair	Dem	CIBIC+ (1-7)	IG1	6	NR	6	4.7 (0.49)	NR	NR	9	5.0 (0.49)	NR	NR, 0.30

Appendix F Table 2. Other Medications and Supplements: Detailed Results for Global Function Outcomes, by Agent

Medication type	Medication	Author, year Quality	Pop cat	Instrument (range)*	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Gonadal steroid	Estrogen	Mulnard, 2000[247] Fair	Dem	CDR (0-5)	IG1	12	1.2 (0.5)	42	NR	0.4 (0.7)	1.0 (0.5)	39	NR	0.2 (0.4)	NR, 0.03
Gonadal steroid	Estrogen		Dem	CDR (0-5)	IG2	12	1.1 (0.5)	39	NR	0.5 (0.6)	1.0 (0.5)	39	NR	0.2 (0.4)	NR, 0.01
Gonadal steroid	Estrogen		Dem	CIBIC+ (1-5)	IG2	12	NR	39	5.2 (0.9)	NR	NR	39	5.0 (1.1)	NR	NR, 0.36
Gonadal steroid	Estrogen		Dem	CIBIC+ (1-7)	IG1	12	NR	42	5.1 (0.9)	NR	NR	39	5.0 (1.1)	NR	NR, 0.66
Gonadal steroid	Estrogen		Dem	CIBIC+ (D)	IG1	12	NA	42	33 (78.6)‖	NR	NA	39	28 (72.0)‖	NR	NR, 0.73
Gonadal steroid	Estrogen		Dem	CIBIC+ (D)	IG2	12	NA	39	31 (79.5)‖	NR	NA	39	28 (72.0)‖	NR	NR, 0.73
Gonadal steroid	Estrogen plus progestin	Valen-Sendstad, 2010[248] Fair	Dem	GDS (1-7)	IG1	12	4.2 (0.6)	29	5.1 (0.7)	NR	4.4 (0.6)	26	5.0 (0.7)	NR	MDC (SD)=0.1 (0.6), 0.43
Gonadal steroid	Estrogen	Wang, 2000[249] Fair	Dem	CDR (0-3)	IG1	3	1.3 (0.5)	25	NR	0.0 (0.4)	1.2 (0.4)	25	NR	0.1 (0.4)	NR, 0.366
Gonadal steroid	Estrogen		Dem	CIBIC+ (1-7)	IG1	3	NR	25	NR	-0.2 (1.0)	NR	25	NR	-0.2 (0.8)	NR, 0.944
Dietary supplement	B vitamins (including folic acid)	Aisen, 2008[250] Good	Dem	CDR-SB (0-18)	IG1	6	5.61 (2.7)	231	0.69 (1.67)	NR	5.85 (2.9)	159	0.79 (2.9)	NR	NR, 0.57
Dietary supplement	B vitamins (including folic acid)		Dem	CDR-SB (0-18)	IG1	12	5.61 (2.7)	214	1.5 (1.92)	NR	5.85 (2.9)	144	1.6 (2.12)	NR	NR, 0.57
Dietary supplement	B vitamins (including folic acid)		Dem	CDR-SB (0-18)	IG1	18	5.61 (2.7)	200	2.58 (2.45)	NR	5.85 (2.9)	139	2.51 (2.57)	NR	NR, 0.57
Dietary Supplement	B vitamins (including folic acid)	Connelly, 2008[251] Fair	Dem	NR	IG1	6	NA	28	20 (71.4)**	NR	NA	21	8 (38.1)**	NR	NR, 0.02
Dietary supplement	Omega-3 fatty acids	Freund-Levi, 2006[253] Fair	Dem	CDR (0-3)	IG1	6	1.0 (NR)	91	1.1 (NR)	NR	1.1 (NR)	87	1.1 (NR)	NR	NR
Dietary supplement	Omega-3 fatty acids		Dem	CDR-SB (0-18)	IG1	6	5.8 (NR)	91	6.2 (NR)	NR	6.0 (NR)	87	6.5 (NR)	NR	NR

Appendix F Table 2. Other Medications and Supplements: Detailed Results for Global Function Outcomes, by Agent

Medication type	Medication	Author, year Quality	Pop cat	Instrument (range)*	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Dietary supplement	Vitamin E	Petersen, 2005[194] Fair	MCI	CDR-SB (0-18)	IG2	6	1.78 (0.8)	NR	NR	0.17 (0.70)	1.87 (0.8)	NR	NR	0.14 (0.86)	NR
Dietary supplement	Vitamin E		MCI	CDR-SB (0-18)	IG2	12	1.78 (0.8)	NR	NR	0.51 (1.21)	1.87 (0.8)	NR	NR	0.40 (1.28)	NR
Dietary supplement	Vitamin E		MCI	CDR-SB (0-18)	IG2	18	1.78 (0.8)	NR	NR	0.75 (1.44)	1.87 (0.8)	NR	NR	0.72 (1.55)	NR
Dietary supplement	Vitamin E		MCI	CDR-SB (0-18)	IG2	24	1.78 (0.8)	NR	NR	1.02 (1.76)	1.87 (0.8)	NR	NR	0.97 (1.76)	NR
Dietary supplement	Vitamin E		MCI	CDR-SB (0-18)	IG2	30	1.78 (0.8)	NR	NR	1.26 (1.89)	1.87 (0.8)	NR	NR	1.26 (2.15)	NR
Dietary supplement	Vitamin E		MCI	CDR-SB (0-18)	IG2	36	1.78 (0.8)	185	NR	1.67 (2.18)	1.87 (0.8)	193	NR	1.64 (2.55)	NR
Dietary supplement	Vitamin E		MCI	GDS (1-7)	IG2	6	2.64 (0.6)	NR	NR	0.11 (0.49)	2.72 (0.6)	NR	NR	0.07 (0.53)	NR
Dietary supplement	Vitamin E		MCI	GDS (1-7)	IG2	12	2.64 (0.6)	NR	NR	0.21 (0.61)	2.72 (0.6)	NR	NR	0.15 (0.65)	NR
Dietary supplement	Vitamin E		MCI	GDS (1-7)	IG2	18	2.64 (0.6)	NR	NR	0.27 (0.73)	2.72 (0.6)	NR	NR	0.27 (0.73)	NR
Dietary supplement	Vitamin E		MCI	GDS (1-7)	IG2	24	2.64 (0.6)	NR	NR	0.42 (0.80)	2.72 (0.6)	NR	NR	0.38 (0.81)	NR
Dietary supplement	Vitamin E		MCI	GDS (1-7)	IG2	30	2.64 (0.6)	NR	NR	0.51 (0.85)	2.72 (0.6)	NR	NR	0.48 (0.87)	NR
Dietary supplement	Vitamin E		MCI	GDS (1-7)	IG2	36	2.64 (0.6)	185	NR	0.64 (0.96)	2.72 (0.6)	193	NR	0.56 (0.99)	NR
Dietary supplement	Omega-3 fatty acids	Quinn, 2010[256] Fair	Dem	CDR-SB (0-18)	IG1	6	5.61 (2.62)	216	NR	1.2 (0.9, 1.5)††	5.77 (2.61)	148	NR	1.1 (0.8, 1.4)††	NR
Dietary supplement	Omega-3 fatty acids		Dem	CDR-SB (0-18)	IG1	12	5.61 (2.62)	191	NR	1.8 (1.5, 2.1)††	5.77 (2.61)	137	NR	2.0 (1.6, 2.4)††	NR
Dietary supplement	Omega-3 fatty acids		Dem	CDR-SB (0-18)	IG1	18	5.61 (2.62)	177	NR	2.87 (2.44, 3.30)††	5.77 (2.61)	127	NR	2.93 (2.44, 3.42)††	NR, 0.68
Dietary supplement	Vitamin E	Sano, 1997[257] Good	Dem	CDR (D)	IG1	24	NA	85	41 (48.2)‡‡	NR	NA	84	43 (51.2)‡‡	NR	NS

* Lower scores indicate better outcomes for all instruments
† Least squares mean
‡ Standard error
§ Least squares mean change
ǁ Number (%) of participants demonstrating functional deterioration (CIBIC + score 5-7)
¶ Number (%) of participants demonstrating minimal, moderate, or marked improvement (CIBIC+ score ≤3)
# New study

Appendix F Table 2. Other Medications and Supplements: Detailed Results for Global Function Outcomes, by Agent

** Number (%) of participants who improved or had no deterioration in MMSE score, as well as evidence of global function improvement on the basis of behavioral and/or functional assessment
†† 95% CI
‡‡ Number (%) of participants receiving a score of 3 on the CDR

Abbreviations: BL = baseline; CDR = Clinical Dementia Rating Scale; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; CG = control group; CI = confidence interval; CIBIC+ = Clinician's Interview-Based Impression of Change with caregiver's input; D = dichotomized; Dem = dementia; ES = effect size; FU = followup; GDS = Global Deterioration Scale; HMG-CoA = β-Hydroxy β-methylglutaryl-CoA; IG = intervention group; Int arm = intervention arm; LSM = least squares mean; MCI = mild cognitive impairment; MD = mean difference; MDC = mean difference in change; mo. = months; Pop cat = population category; NA = not applicable; NR = not reported; NS = not statistically significant; NSAID = Nonsteroidal Anti-inflammatory Drug; SD = standard deviation; SE = standard error

Appendix F Table 3. Other Medications and Supplements: Detailed Results for Physical Function Outcomes, by Agent

Medication type	Medication	Author, year Quality	Pop cat	ADL or ADL, (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Antihypertensive	Discontinuation of antihypertensive	Moonen, 2015*[235] Fair	MCI	ADL/IADL (GARS, 18-72, ↓)	IG1	4	23† (NR)	180	NR	-0.77 (-1.33, -0.20)‡	22† (NR)	176	NR	-0.05 (-0.62, 0.52)‡	NR, 0.08
HMG-CoA reductase inhibitor	Atorvastatin	Feldman, 2010[236] Fair	Dem	ADL/IADL (ADFACS, 0-54, ↓)	IG1	6	13.2 (8.9)	285	NR	2.51§ (0.30)‖	13.1 (8.5)	311	NR	2.06§ (0.29)‖	LSM change (SE)=0.45 (0.41), 0.27
HMG-CoA reductase inhibitor	Atorvastatin		Dem	ADL/IADL (ADFACS, 0-54, ↓)	IG1	11	13.2 (8.9)	233	NR	4.95§ (0.43)‖	13.1 (8.5)	279	NR	4.55§ (0.40)‖	LSM change (SE)=0.40 (0.58), 0.49
HMG-CoA reductase inhibitor	Atorvastatin		Dem	ADL/IADL (ADFACS, 0-54, ↓)	IG1	18	13.2 (8.9)	214	NR	7.36§ (0.54)‖	13.1 (8.5)	256	NR	6.91§ (0.50)‖	LSM change (SE)=0.45 (0.74), 0.54
HMG-CoA reductase inhibitor	Simvastatin	Sano, 2011[237] Fair	Dem	ADL (ADCS-ADL, 0-27, ↓)	IG1	3	67.2 (10.0)	204	NR	-1.54 (7.44)	68.6 (10.4)	202	NR	-1.2 (6.09)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	ADL (ADCS-ADL, 0-27, ↓)	IG1	6	67.2 (10.0)	204	NR	-3.66 (8.18)	68.6 (10.4)	202	NR	-3.95 (8.42)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	ADL (ADCS-ADL, 0-27, ↓)	IG1	12	67.2 (10.0)	204	NR	-7.45 (10.18)	68.6 (10.4)	202	NR	-6.21 (10.94)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	ADL (Dependency Scale, 0-5, ↓)	IG1	3	5.2 (2.3)	204	NR	-0.04 (0.85)	4.9 (2.3)	202	NR	-0.15 (0.87)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	ADL (Dependency Scale, 0-5, ↓)	IG1	6	5.2 (2.3)	204	NR	-0.1 (1.04)	4.9 (2.3)	202	NR	-0.21 (0.83)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	ADL (Dependency Scale, 0-5, ↓)	IG1	12	5.2 (2.3)	204	NR	-0.26 (1.02)	4.9 (2.3)	202	NR	-0.36 (0.96)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	ADL (Dependency Scale, 0-5, ↓)	IG1	18	5.2 (2.3)	204	NR	-0.48 (1.09)	4.9 (2.3)	202	NR	-0.53 (1.1)	NS
HMG-CoA reductase inhibitor	Simvastatin	Sano, 2011[237] Fair	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	18	67.2 (10.0)	204	NR	-10.47 (13.37)	68.6 (10.4)	202	NR	-9.62 (13.86)	NS

Appendix F Table 3. Other Medications and Supplements: Detailed Results for Physical Function Outcomes, by Agent

Medication type	Medication	Author, year Quality	Pop cat	ADL or ADL, (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
HMG-CoA reductase inhibitor	Atorvastatin	Sparks, 2005[239] Fair	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	38.8 (1.93)‖	NR	37.2 (2.10)‖	NR	41.2 (1.85)‖	NR	33.6 (2.35)‖	NR	NR, 0.263
HMG-CoA reductase inhibitor	Atorvastatin		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	12	38.8 (1.93)‖	NR	31.2 (2.25)‖	NR	41.2 (1.85)‖	NR	27.6 (2.33)‖	NR	NR, 0.226
NSAID	Naproxen	Aisen, 2003[240] Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	12	60.0 (13.1)	118	51.3 (16.3)	-8.7 (10.5)	62.8 (11.4)	111	51.3 (16.3)	-11.5 (11.2)	NR, 0.14
NSAID	Ibuprofen	Pasqualetti, 2009[242] Fair	Dem	ADL (Katz Index, 0-6, ↑)	IG1	12	NR	66	NR	-0.5 (0.2)‖	NR	66	NR	-0.4 (0.2)‖	MDC (95% CI)=-0.1 (-0.6, 0.4), 0.756
NSAID	Ibuprofen	Pasqualetti, 2009[242] Fair	Dem	IADL (Lawton and Brody IADL, 0-8, ↑)	IG1	12	NR	66	NR	-0.5 (0.2)‖	NR	66	NR	-0.7 (0.2)‖	MDC (95% CI)=0.2 (-0.3, 0.6), 0.483
Gonadal steroid	Estrogen	Henderson, 2000[245] Fair	Dem	IADL (Lawton and Brody IADL, 0-54, ↑)	IG1	4	14.7 (2.0)‖	18	17.6 (2.6)‖	2.9 (1.1)‖	13.2 (2.0)‖	18	16.1 (2.3)‖	2.9 (1.5)‖	MDC=0.0, >0.1
Gonadal steroid	Estrogen	Henderson, 2015*[244] Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	63.5 (12.4)	21	NR	-6.9 (NR)	58.3 (14.8)	21	NR	-0.3 (NR)	ES (95% CI)=-0.48 (-0.82, -0.15), 0.006
Gonadal steroid	Estrogen		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	12	63.5 (12.4)	21	NR	-9.1 (NR)	58.3 (14.8)	21	NR	-4.5 (NR)	ES (95% CI)=-0.34 (-0.84, 0.18), NR
Gonadal steroid	Estrogen	Mulnard, 2000[247] Fair	Dem	ADL (Dependency Scale, 0-5, ↓)	IG1	12	NR	42	NR	0.4 (0.8)	NR	39	NR	0.4 (1.1)	NR, 0.59
Gonadal steroid	Estrogen		Dem	ADL (Dependency Scale, 0-5, ↓)	IG2	12	NR	39	NR	0.5 (1.0)	NR	39	NR	0.4 (1.1)	NR, 0.21
Gonadal steroid	Estrogen plus progestin	Valen-Sendstad, 2010[248] Fair	Dem	ADL (Barthel Index, 0-20, ↑)	IG1	12	19.4 (1.2)	29	18.5 (3.1)	NR	19.2 (1.2)	26	19.1 (1.3)	NR	MDC (SD)=-0.5 (1.8), 0.36
Dietary supplement	B vitamins (including folic acid)	Aisen, 2008[250] Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	61.31 (11.6)	231	NR	-3.28 (7.99)	59.66 (12.9)	160	NR	-2.86 (7.8)	NR

Appendix F Table 3. Other Medications and Supplements: Detailed Results for Physical Function Outcomes, by Agent

Medication type	Medication	Author, year Quality	Pop cat	ADL or ADL, (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Dietary supplement	B vitamins (including folic acid)		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	12	61.31 (11.6)	220	NR	-7.38 (9.97)	59.66 (12.9)	147	NR	-7.82 (10.0)	NR
Dietary supplement	B vitamins (including folic acid)		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	18	61.31 (11.6)	206	NR	-10.96 (12.36)	59.66 (12.9)	140	NR	-10.0 (11.09)	NR
Dietary supplement	B vitamins (including folic acid)	Connelly, 2008[251] Fair	Dem	IADL (NOSGER IADL subscale, 5-25, ↓)	IG1	6	18.7 (4.61)	23	NR	0.61 (3.6)	18.22 (4.28)	18	NR	-2.06 (4.17)	NR, 0.03
Dietary supplement	Vitamin E	Dysken, 2014*[222] Good	Dem	ADL/IADL (ADCS-ADL, 0-78)	IG2	6	56.6 (14.9)	134	NR	-1.73§ (-3.61, 0.15)‡	56.8 (13.7)	135	NR	-4.54§ (-6.42, -2.68)‡	NR
Dietary supplement	Vitamin E		Dem	ADL/IADL (ADCS-ADL, 0-78)	IG2	12	56.6 (14.9)	122	NR	-4.30§ (-6.69, -1.94)‡	56.8 (13.7)	112	NR	-8.14§ (-10.5, -5.73)‡	NR
Dietary supplement	Vitamin E		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG2	18	56.6 (14.9)	103	NR	-8.03§ (-10.7, -5.25)‡	56.8 (13.7)	96	NR	-10.2§ (-13.0, -7.40)‡	NR
Dietary supplement	Vitamin E		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG2	24	56.6 (14.9)	88	NR	-11.9§ (-15.2, -8.64)‡	56.8 (13.7)	77	NR	-16.2§ (-19.6, -12.8)‡	NR
Dietary supplement	Vitamin E		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG2	30	56.6 (14.9)	66	NR	-15.9§ (-19.7, -12.0)‡	56.8 (13.7)	54	NR	-19.7§ (-23.7, -15.6)‡	NR
Dietary supplement	Vitamin E		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG2	36	56.6 (14.9)	51	NR	-19.7§ (-24.3, -15.1)‡	56.8 (13.7)	41	NR	-24.8§ (-29.7, -19.9)‡	NR
Dietary supplement	Vitamin E		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG2	42	56.6 (14.9)	39	NR	-25.2§ (-30.3, -20.3)‡	56.8 (13.7)	33	NR	-28.1§ (-33.5, -22.7)‡	NR
Dietary supplement	Vitamin E		Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG2	48	56.6 (14.9)	140	NR	-13.81§ (1.11)‖	56.8 (13.7)	140	NR	-16.96§ (1.11)‖	MDC (95% CI)=3.15 (0.92, 5.39), 0.03
Dietary supplement	Omega-3 fatty acids	Freund-Levi, 2006[253] Fair	Dem	ADL/IADL (DAD, 0-46, ↑)	IG1	6	33.5 (NR)	89	31.8 (NR)	NR	33.1 (NR)	85	30.5 (NR)	NR	NR, 0.34
Dietary supplement	Vitamin E	Petersen, 2005[194] Fair	MCI	IADL (ADCS-MCI-ADL, 0-53, ↑)	IG2	6	45.82 (4.6)	NR	NR	-0.34 (4.29)	45.87 (5.2)	NR	NR	-1.06 (4.54)	NR
Dietary supplement	Vitamin E		MCI	IADL (ADCS-MCI-ADL, 0-53, ↑)	IG2	12	45.82 (4.6)	NR	NR	-1.08 (4.90)	45.87 (5.2)	NR	NR	-1.44 (5.00)	NR
Dietary supplement	Vitamin E		MCI	IADL (ADCS-MCI-ADL, 0-53, ↑)	IG2	18	45.82 (4.6)	NR	NR	-2.13 (5.76)	45.87 (5.2)	NR	NR	-2.34 (6.02)	NR

Appendix F Table 3. Other Medications and Supplements: Detailed Results for Physical Function Outcomes, by Agent

Medication type	Medication	Author, year Quality	Pop cat	ADL or ADL, (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Dietary supplement	Vitamin E	Petersen, 2005[194] Fair	MCI	IADL (ADCS-MCI-ADL, 0-53, ↑)	IG2	24	45.82 (4.6)	NR	NR	-2.84 (6.16)	45.87 (5.2)	NR	NR	-3.43 (6.73)	NR
Dietary supplement	Vitamin E		MCI	IADL (ADCS-MCI-ADL, 0-53, ↑)	IG2	30	45.82 (4.6)	NR	NR	-4.16 (7.46)	45.87 (5.2)	NR	NR	-5.00 (8.05)	NR
Dietary supplement	Vitamin E		MCI	IADL (ADCS-MCI-ADL, 0-53, ↑)	IG2	36	45.82 (4.6)	185	NR	-5.63 (8.75)	45.87 (5.2)	193	NR	-6.39 (8.99)	NR
Dietary supplement	Omega-3 fatty acids	Phillips, 2015*[255] Fair	MCI + Dem	ADL/IADL (Bristol ADL, 0-60, ↓)	IG1	4	2.62 (5.28)	37	3.35 (7.10)	NR	4.72 (7.34)	39	5.38 (8.07)	NR	NR, 0.595
Dietary supplement	Omega-3 fatty acids	Quinn, 2010[256] Fair	Dem	ADL (ADCS-ADL, 0-27, ↓)	IG1	6	NR	219	NR	-4.5 (-5.8, -3.4)‡	NR	147	NR	-3.2 (-4.6, -2.0)‡	NR
Dietary supplement	Omega-3 fatty acids		Dem	ADL (ADCS-ADL, 0-27, ↓)	IG1	12	NR	192	NR	-6.4 (-8.0, -5.2)‡	NR	141	NR	-6.7 (-8.3, -5.1)‡	NR
Dietary supplement	Omega-3 fatty acids		Dem	ADL (ADCS-ADL, 0-27, ↓)	IG1	18	NR	178	NR	-11.51 (-13.45, -9.57)‡	NR	130	NR	-10.43 (-12.45, -8.41)‡	NR, 0.38
Dietary supplement	Vitamin E	Sano, 1997[257] Good	Dem	ADL (Dependency Scale, D)	IG1	24	NA	85	65 (76.5)¶	NR	NA	84	72 (85.7)¶	NR	NR, 0.039
Dietary supplement	Omega-3 fatty acids	Shinto, 2014*[258] Fair	Dem	ADL (ADCS-ADL, 0-27, ↓)	IG1	12	2.2 (0.3)‖	11	NR	2.5 (1.0)‖	3.3 (1.0)‖	11	NR	2.9 (0.7)‖	NR, 0.82
Dietary supplement	Omega-3 and LA		Dem	ADL (ADCS-ADL, 0-27, ↓)	IG2	12	1.5 (0.6)‖	12	NR	1.3 (0.8)‖	3.3 (1.0)‖	11	NR	2.9 (0.7)‖	NR, 0.15
Dietary supplement	Omega-3 fatty acids		Dem	IADL (ADCS-ADL, 0-14, ↓)	IG1	6	10.8 (1.1)‖	11	NR	1.29 (0.75)‖	10.0 (1.8)‖	11	NR	1.53 (0.75)‖	NR
Dietary supplement	Omega-3 fatty acids		Dem	IADL (ADCS-ADL, 0-14, ↓)	IG1	12	10.8 (1.1)‖	12	NR	0.7 (1.0)‖	10.0 (1.8)‖	11	NR	4.2 (0.9)‖	NR, <0.01
Dietary supplement	Omega-3 and LA		Dem	IADL (ADCS-ADL, 0-14, ↓)	IG2	6	6.8 (1.9)‖	12	NR	1.51 (0.6)‖	10.0 (1.8)‖	11	NR	1.53 (0.6)‖	NR, NR
Dietary supplement	Omega-3 and LA		Dem	IADL (ADCS-ADL, 0-14, ↓)	IG2	12	6.8 (1.9)‖	12	NR	0.9 (1.1)‖	10.0 (1.8)‖	11	NR	4.2 (1.1)‖	NR, 0.01
Dietary supplement	Multivitamin	Sun, 2007[260] Fair	Dem	ADL (Barthel Index, 0-6, ↑)	IG1	24	NR	45	NR	-0.33 (-1.03, 0.36)‡	NR	44	NR	-0.19 (-0.57, 0.20)‡	NR, 0.70
Dietary supplement	Multivitamin		Dem	IADL (Lawton and Brody IADL, 0-8, ↑)	IG1	6	NR	45	NR	0.04 (-1.01, 1.08)‡	NR	44	NR	0.04 (-0.41, 0.33)‡	NR, 0.89
Dietary supplement	Omega-3 fatty acids	Yurko-Mauro, 2010[261] Good	MCI	ADL (ADCS-ADL, 0-27, ↓)	IG1	6	NR	241	NR	-2.0 (0.3)‖	NR	242	NR	-1.7 (0.3)	NR, <0.59

Appendix F Table 3. Other Medications and Supplements: Detailed Results for Physical Function Outcomes, by Agent

* New study
† Median
‡ 95% CI
§ Least squares mean change
‖ Standard error
¶ Number (%) of patients receiving a higher score on Dependence Scale at followup

Abbreviations: ADL = Activities of Daily Living; ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living 23 items; ADFACS = Alzheimer's Disease Functional Assessment and Change Scale; BL = baseline; CG = control group; CI = confidence interval; D = dichotomized; DAD = Disability Assessment for Dementia; Dem = dementia; ES = effect size; FU = followup; GARS = Groningen Activity Restriction Scale; HMG-CoA = β-Hydroxy β-methylglutaryl-CoA; IADL = Instrumental Activities of Daily Living; IG = intervention group; Int arm = intervention arm; Katz Index = Katz Index of Independence in Activities of Daily Living; LSM = least squares mean; MCI = mild cognitive impairment; MDC = mean difference in change; mo. = months; n = number of participants analyzed; NOSGER = Nurses' Observation Scale for Geriatric Patients scale; NA = not applicable; NR = not reported; NS = Not statistically significant; NSAID = Nonsteroidal Anti-inflammatory Drug; Pop cat = population category; SD = standard deviation; SE = standard error

Appendix F Table 4. Other Medications and Supplements: Detailed Results for Mental Health and Neuropsychiatric Symptom Outcomes, by Agent

Medication type	Medication	Author, year Quality	Pop cat	Symptom (Instrument, range†)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Antihypertensive	Discontinuation of antihypertensive	Moonen, 2015*[235] Fair	MCI	Dep (GDS-15, 0-15)	IG1	4	1‡ (NR)	180	NR	-0.05 (-0.29, 0.19)§	1‡ (NR)	176	NR	-0.19 (-0.43, 0.05)§	NR, 0.41
HMG-CoA reductase inhibitor	Atorvastatin	Feldman, 2010[236] Fair	Dem	NPS (NPI-12, 0-144)	IG1	6	9.7 (11.5)	285	NR	1.01‖ (0.52)¶	9.6 (10.3)	309	NR	0.42‖ (0.50)¶	LSM change (SE)=0.59 (0.72), 0.41
HMG-CoA reductase inhibitor	Atorvastatin		Dem	NPS (NPI-12, 0-144)	IG1	11	9.7 (11.5)	231	NR	1.03 (0.66)¶	9.6 (10.3)	277	NR	1.89 (0.61)¶	LSM change (SE)=-0.86 (0.90), 0.34
HMG-CoA reductase inhibitor	Atorvastatin		Dem	NPS (NPI-12, 0-144)	IG1	18	9.7 (11.5)	215	NR	2.15‖ (0.88)¶	9.6 (10.3)	255	NR	3.25‖ (0.81)¶	LSM change (SE)=-1.1 (1.20), 0.36
HMG-CoA reductase inhibitor	Simvastatin	Sano, 2011[257] Fair	Dem	NPS (NPI-12, 0-144)	IG1	3	9.2 (10.5)	204	NR	-0.64 (8.61)	7.8 (8.3)	202	NR	0.21 (8.02)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	NPS (NPI-12, 0-144)	IG1	6	9.2 (10.5)	204	NR	-0.09 (9.61)	7.8 (8.3)	202	NR	1.26 (9.16)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	NPS (NPI-12, 0-144)	IG1	12	9.2 (10.5)	204	NR	1.95 (10.64)	7.8 (8.3)	202	NR	3.60 (10.38)	NS
HMG-CoA reductase inhibitor	Simvastatin		Dem	NPS (NPI-12, 0-144)	IG1	18	9.2 (10.5)	204	NR	3.21 (12.71)	7.8 (8.3)	202	NR	3.78 (10.73)	NS
HMG-CoA reductase inhibitor	Atorvastatin	Sparks, 2005[239] Fair	Dem	Dep (GDS-15, 0-15)	IG1	12	5.25 (0.69)¶	25	3.75 (1.91)¶	NR	6.61 (0.88)¶	21	8.16 (1.76)¶	NR	NR, 0.04
NSAID	Naproxen	Aisen, 2003[240] Good	Dem	NPS (NPI-12, 0-144)	IG1	12	9.4 (9.6)	118	13.1 (14.4)	3.7 (12.5)	8.7 (10.6)	111	12.2 (12.8)	3.4 (11.9)	NR, 0.76
NSAID	Indomethacin	de Jong, 2008[241] Fair	Dem	NPS (NPI-10, 0-120)	IG1	6	11.2 (12.0)	20	NR	1.7 (14.0)	7.1 (6.7)	23	NR	-0.3 (4.9)	MDC (95% CI)=3.6 (-2.9, 10.1), NR
NSAID	Indomethacin		Dem	NPS (NPI-10, 0-120)	IG1	12	11.2 (12.0)	19	NR	3.2 (18.1)	7.1 (6.7)	19	NR	9.4 (14.0)	MDC (95% CI)=-4.6 (-15.8, 6.6), NR
NSAID	Ibuprofen	Pasqualetti, 2009[242] Fair	Dem	Dep (GDS, 0-30)	IG1	12	NR	66	NR	0.2 (0.5)¶	NR	66	NR	-0.1 (0.5)¶	MDC (95% CI)=0.4 (-0.8, 1.5), 0.545

Appendix F Table 4. Other Medications and Supplements: Detailed Results for Mental Health and Neuropsychiatric Symptom Outcomes, by Agent

Medication type	Medication	Author, year Quality	Pop cat	Symptom (Instrument, range†)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
NSAID	Ibuprofen		Dem	NPS (NPI-12, 0-144)	IG1	12	NR	66	NR	-2.2 (2.0)¶	NR	66	NR	-1.3 (2.2)¶	MDC (95% CI)=-0.9 (-5.3, 3.4), 0.669
NSAID	Celecoxib	Soininen, 2007[243] Fair	Dem	NPS (BEHAVE-AD1, 0-75)	IG1	3	4.6 (4.8)	266	NR	0.25‖ (NR)	5.0 (5.5)	124	NR	0.30 (NR)	NR, 0.897
NSAID	Celecoxib		Dem	NPS (BEHAVE-AD1, 0-75)	IG1	6	4.6 (4.8)	275	NR	1.01‖ (NR)	5.0 (5.5)	135	NR	0.28‖ (NR)	NR, 0.122
NSAID	Celecoxib		Dem	NPS (BEHAVE-AD1, 0-75)	IG1	12	4.6 (4.8)	276	NR	1.46‖ (NR)	5.0 (5.5)	135	NR	1.18‖ (NR)	NR, 0.655
Gonadal steroid	Estrogen	Henderson, 2000[245] Fair	Dem	Dep (MADRS, 0-60)	IG1	4	9.7 (2.0)¶	18	9.8 (1.8)¶	0.2 (1.6)¶	10.9 (2.1)¶	18	12.0 (2.1)¶	1.1 (1.4)¶	MDC=-0.9, >0.1
Gonadal steroid	Estrogen		Dem	Dep (GDS, 0-30)	IG1	4	17.8 (1.4)¶	18	16.4 (1.9)¶	-1.4 (1.4)¶	16.5 (1.8)¶	18	15.8 (1.9)¶	-0.7 (1.2)¶	MDC=-0.7, >0.1
Gonadal steroid	Estrogen	Henderson, 2015*[244] Good	Dem	NPS (NPI-10, 0-120)	IG1	6	5.2 (6.6)	21	NR	0.7 (NR)	5.8 (7.8)	21	NR	3.1 (NR)	ES (95% CI): -0.35 (-1.04, 0.35), NR
Gonadal steroid	Estrogen		Dem	NPS (NPI-10, 0-120)	IG1	12	5.2 (6.6)	21	NR	2.3 (NR)	5.8 (7.8)	21	NR	2.5 (NR)	ES (95% CI): -0.02 (-0.70, 0.65), NR
Gonadal steroid	Testosterone	Lu, 2006[246] Fair	Dem	Dep (BDI, 0-63)	IG1	6	6.8 (4.3)	4	6.5 (2.5)	-0.3 (3.6)	8.6 (4.9)	7	9.1 (3.8)	0.6 (6.0)	NR, 0.32
Gonadal steroid	Testosterone		Dem	NPS (NPI-10, 0-120)	IG1	6	4.2 (3.5)	5	5.4 (7.6)	1.2 (5.4)	7.8 (7.3)	8	11.1 (17.1)	3.4 (16.4)	NR, 0.74
Gonadal steroid	Testosterone		Dem	NPS (NPI-10, D)	IG1	6	NA	9	4 (44.4)#	NR	NA	9	7 (77.8)#	NR	NR, >0.16
Gonadal steroid	Estrogen	Mulnard, 2000[247] Fair	Dem	Dep (HDRS, 0-52)	IG1	12	3.4 (4.0)	42	NR	0.5 (3.7)	3.8 (4.0)	39	NR	0.03 (3.9)	NR, 0.69
Gonadal steroid	Estrogen		Dem	Dep (HDRS, 0-52)	IG2	12	3.2 (3.0)	39	NR	-0.1 (4.3)	3.8 (4.0)	39	NR	0.03 (3.9)	NR, 0.69
Gonadal steroid	Estrogen plus progestin	Valen-Sendstad, 2010[248] Fair	Dem	Dep (CERAD Depression, 0-9)	IG1	12	1.1 (1.3)	29	1.2 (1.8)	NR	1.6 (1.6)	26	1.2 (1.3)	NR	MDC (SD)=-0.6 (1.3), 0.13
Gonadal steroid	Estrogen plus progestin		Dem	Dep (CERAD Depression, 0-9)**	IG1	12	2.3 (2.0)	29	2.4 (1.9)	NR	3.0 (2.2)	26	3.2 (1.7)	NR	MDC (SD)=-0.4 (2.8), 0.62
Gonadal steroid	Estrogen	Wang, 2000[249] Fair	Dem	Anx (HARS, 0-56)	IG1	3	6.4 (4.7)	25	NR	-0.8 (4.7)	7.2 (4.3)	25	NR	0.4 (2.6)	NR, 0.277
Gonadal steroid	Estrogen		Dem	Dep (HDRS, 0-52)	IG1	3	7.1 (4.5)	25	NR	-1.2 (5.8)	7.5 (4.9)	25	NR	0.4 (4.8)	NR, 0.335

Appendix F Table 4. Other Medications and Supplements: Detailed Results for Mental Health and Neuropsychiatric Symptom Outcomes, by Agent

Medication type	Medication	Author, year Quality	Pop cat	Symptom (Instrument, range†)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Gonadal steroid	Estrogen		Dem	NPS (BEHAVE-AD1, 0-75)	IG1	3	4.9 (5.7)	25	NR	-0.4 (3.8)	4.7 (5.5)	25	NR	-0.8 (5.0)	NR
Dietary supplement	B vitamins (including folic acid)	Aisen, 2008[250] Good	Dem	NPS (NPI-12, 0-144)	IG1	3	6.0‡ (NR)	234	NR	0.71 (6.31)	5.0‡ (NR)	164	NR	0.64 (4.83)	NR
Dietary supplement	B vitamins (including folic acid)		Dem	NPS (NPI-12, 0-144)	IG1	6	6.0‡ (NR)	231	NR	0.97 (10.82)	5.0‡ (NR)	159	NR	1.03 (8.82)	NR
Dietary supplement	B vitamins (including folic acid)		Dem	NPS (NPI-12, 0-144)	IG1	12	6.0‡ (NR)	215	NR	1.03 (10.53)	5.0‡ (NR)	145	NR	1.19 (9.31)	NR
Dietary supplement	B vitamins (including folic acid)		Dem	NPS (NPI-12, 0-144)	IG1	18	6.0‡ (NR)	198	NR	3.31 (12.84)	5.0‡ (NR)	136	NR	2.2 (11.12)	NR
Dietary supplement	B vitamins (including folic acid)	de Jager, 2012[252] Fair	MCI	Dep (GDS, 0-30)	IG1	24	NR	133	NR	-0.073 (3.4)	NR	133	NR	0.018 (3.6)	NS
Dietary supplement	Vitamin E	Dysken, 2014*[222] Good	Dem	NPS (NPI-12, 0-144)	IG2	6	7.5‡ (NR)	133	NR	-1.24‖ (-3.35, 0.87)§	8.0‡ (NR)	135	NR	0.47‖ (-1.62, 2.57)§	NR
Dietary supplement	Vitamin E		Dem	NPS (NPI-12, 0-144)	IG2	12	7.5‡ (NR)	122	NR	-1.04‖ (-3.40, 1.34)§	8.0‡ (NR)	112	NR	1.08‖ (-1.36, 3.53)§	NR
Dietary supplement	Vitamin E		Dem	NPS (NPI-12, 0-144)	IG2	18	7.5‡ (NR)	103	NR	0.93‖ (-1.81, 3.68)§	8.0‡ (NR)	96	NR	4.05‖ (1.26, 6.87)§	NR
Dietary supplement	Vitamin E		Dem	NPS (NPI-12, 0-144)	IG2	24	7.5‡ (NR)	87	NR	2.16‖ (-1.25, 5.58)§	8.0‡ (NR)	75	NR	3.59‖ (0.004, 7.19)§	NR
Dietary supplement	Vitamin E		Dem	NPS (NPI-12, 0-144)	IG2	30	7.5‡ (NR)	64	NR	3.20‖ (-0.13, 6.55)§	8.0‡ (NR)	55	NR	1.68‖ (-1.88, 5.21)§	NR
Dietary supplement	Vitamin E	Dysken, 2014*[222] Good	Dem	NPS (NPI-12, 0-144)	IG2	36	7.5‡ (NR)	51	NR	2.14‖ (-1.73, 6.01)§	8.0‡ (NR)	41	NR	0.60‖ (-3.63, 4.83)§	NR
Dietary supplement	Vitamin E		Dem	NPS (NPI-12, 0-144)	IG2	42	7.5‡ (NR)	39	NR	0.82‖ (-4.35, 6.01)§	8.0‡ (NR)	33	NR	3.63‖ (-2.01, -9.31)§	NR

Appendix F Table 4. Other Medications and Supplements: Detailed Results for Mental Health and Neuropsychiatric Symptom Outcomes, by Agent

Medication type	Medication	Author, year Quality	Pop cat	Symptom (Instrument, range†)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Dietary supplement	Vitamin E		Dem	NPS (NPI-12, 0-144)	IG2	48	7.5‡ (NR)	140	NR	0.79‖ (1.00)¶	8.0‡ (NR)	140	NR	2.26‖ (1.01)¶	MDC (95% CI)=-1.46 (-3.55, 0.63), 0.94
Dietary supplement	Omega-3 fatty acids	Freund-Levi, 2006[253] Fair	Dem	Dep (MADRS, 0-30)	IG1	6	1.8 (NR)	89	1.5 (NR)	NR	1.9 (NR)	85	1.6 (NR)	NR	NR, 0.49
Dietary supplement	Omega-3 fatty acids		Dem	NPS (NPI-12, 0-144)	IG1	6	15.6 (NR)	89	16.6 (NR)	NR	14.9 (NR)	85	16.0 (NR)	NR	NR, 0.45
Dietary supplement	B vitamins (including folic acid)	Kwok, 2011[254] Fair	Dem	Dep (CSDD, 0-38)	IG1	24	1.9 (2.5)	59	NR	0†† (-2, 0)	1.8 (2.5)	53	NR	0†† (-2, 1)	NR, 0.436
Dietary supplement	B vitamins (including folic acid)		Dem	NPS (NPI-12, 0-144)	IG1	24	7.7 (11.4)	59	NR	0†† (-3, 7)	9.0 (11.0)	53	NR	0†† (-2.5, 7)	NR, 0.606
Dietary supplement	Omega-3 fatty acids	Phillips, 2015*[255] Fair	MCI + Dem	Dep (BASDEC, 0-21)	IG1	4	2.7 (2.4)	37	2.3 (2.9)	NR	2.3 (2.0)	39	2.1 (2.5)	NR	NR, 0.548
Dietary supplement	Omega-3 fatty acids	Quinn, 2010[256] Fair	Dem	NPS (NPI-12, 0-144)	IG1	6	NR	219	NR	1.8 (0.4, 3.3)§	NR	146	NR	1.0 (-0.8, 2.6)§	NR
Dietary supplement	Omega-3 fatty acids		Dem	NPS (NPI-12, 0-144)	IG1	12	NR	192	NR	0.7 (-0.9, 2.1)§	NR	141	NR	2.7 (0.8, 4.9)§	NR
Dietary supplement	Omega-3 fatty acids		Dem	NPS (NPI-12, 0-144)	IG1	18	NR	176	NR	2.93 (0.92, 4.94)§	NR	129	NR	5.09 (2.49, 7.69)§	MDC (95% CI)=NR (NR, NR), 0.11
Dietary supplement	Omega-3 fatty acids - DHA	Sinn, 2012[259] Fair	MCI	Dep (GDS-15, 0-15)	IG1	6	3.19 (3.17)	18	-0.68 (0.30)	NR	3.15 (2.08)	14	0.69 (0.61)	NR	ES (SE) (95% CI): -1.40 (0.53)(-2.47, -0.32), 0.01
Dietary supplement	Omega-3 fatty acids - EPA	Sinn, 2012[259] Fair	MCI	Dep (GDS-15, 0-15)	IG2	6	4.40 (2.92)	17	-0.52 (0.30)	NR	3.15 (2.08)	14	0.69 (0.61)	NR	ES (SE) (95% CI): -1.23 (0.56)(-2.37, -0.09), 0.04
Dietary supplement	Omega-3 fatty acids	Yurko-Mauro, 2010[261] Good	MCI	Dep (GDS, 0-30)	IG1	6	1.3 (1.2)	241	1.4 (1.6)	0.1 (0.10)¶	1.3 (1.3)	242	1.3 (1.5)	0.0 (0.08)¶	MDC (SE)=0.1 (0.12), 0.230

* New study

† Lower scores indicate better outcomes for all instruments

Appendix F Table 4. Other Medications and Supplements: Detailed Results for Mental Health and Neuropsychiatric Symptom Outcomes, by Agent

‡ Median
§ 95% CI
‖ Least squares mean change
¶ Standard error
# Number (%) of participants displaying at least 1 neuropsychiatric symptom of mild severity based on NPI
** Caregiver-reported
†† Median change (IQR)

Abbreviations: Anx = anxiety; BASDEC = Brief Assessment Schedule Depression Cards; BDI = Beck Depression Inventory; BEHAVE-AD1 = Behavioral Pathology in Alzheimer's Disease – Part 1; BL = baseline; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CG = control group; CI = confidence interval; CSDD = Cornell Scale for Depression in Dementia; Dem = dementia; Dep = depression; ES = effect size; FU = followup; GDS = Geriatric Depression Scale; GDS-15 = Geriatric Depression Scale-15 Item; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; HMG-CoA = β-Hydroxy β-methylglutaryl-CoA; IG = intervention group; Int arm = intervention arm; LSM = least squares mean; MADRS = Montgomery-Åsberg Depression Rating Scale; MCI = mild cognitive impairment; MDC = mean difference in change; mo. = months; NPI-10 = Neuropsychiatric Inventory-10 item; NPI-12 = Neuropsychiatric Inventory-12 item; NPS = Composite neuropsychiatric symptoms; NR = not reported; NS = not statistically significant; NSAID = Nonsteroidal Anti-inflammatory Drug; Pop cat = population category; SD = standard deviation; SE = standard error

Appendix F Table 5. Other Medications and Supplements: Detailed Results for Harms, by Medication Type

Medication type	Intervention	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
Antihypertensive	Discontinuation of antihypertensive	Moonen, 2015*[235] Fair	Serious adverse events	IG1	4	199	13†	186	13†	NR
HMG-CoA reductase inhibitor	Atorvastatin	Feldman, 2010[236] Fair	Adverse events	IG1	18	314	272 (86.6)	325	277 (85.2)	NR
HMG-CoA reductase inhibitor	Atorvastatin		Serious adverse events	IG1	18	314	50 (15.9)	325	51 (15.7)	NR
HMG-CoA reductase inhibitor	Atorvastatin		Withdrawals due to adverse events	IG1	18	314	56 (17.8)	325	31 (9.5)	NR
HMG-CoA reductase inhibitor	Simvastatin	Sano, 2011[237] Fair	Adverse events	IG1	18	204	189 (92.6)	202	181 (89.6)	NR, 0.91
HMG-CoA reductase inhibitor	Simvastatin		Serious adverse events	IG1	18	204	56 (27.5)	202	54 (26.7)	NR, 0.91
HMG-CoA reductase inhibitor	Simvastatin		Withdrawals due to adverse events	IG1	18	204	13 (6.4)	202	16 (7.9)	NR
HMG-CoA reductase inhibitor	Simvastatin	Simons, 2002[238] Fair	Withdrawals due to adverse events	IG1	6	24	2 (8.3)	20	0 (0.0)	NR
NSAID	Naproxen	Aisen, 2003[240] Good	Withdrawals due to adverse events	IG1	12	118	10 (8.5)	111	11 (9.9)	NR
NSAID	Indomethacin	de Jong, 2008[241] Fair	Serious adverse events	IG1	12	26	5 (19.2)	25	1 (4.0)	NR
NSAID	Indomethacin		Withdrawals due to adverse events	IG1	6	26	5 (19.2)	25	0 (0.0)	NR
NSAID	Indomethacin	de Jong, 2008[241] Fair	Withdrawals due to adverse events	IG1	12	20	1 (5.0)	23	0 (0.0)	NR

Appendix F Table 5. Other Medications and Supplements: Detailed Results for Harms, by Medication Type

Medication type	Intervention	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
NSAID	Ibuprofen	Pasqualetti, 2009[242] Fair	Withdrawals due to adverse events	IG1	12	66	7 (10.6)	66	10 (15.2)	NR
NSAID	Celecoxib	Soininen, 2007[243] Fair	Adverse events	IG1	12	285	229 (80.4)	140	105 (75.0)	NR
NSAID	Celecoxib		Serious adverse events	IG1	12	285	73 (25.6)	140	32 (22.9)	NR
NSAID	Celecoxib		Withdrawals due to adverse events	IG1	12	285	34 (11.9)	140	15 (10.7)	NR
Gonadal steroid	Estrogen	Henderson, 2015*[244] Good	Adverse events	IG1	12	21	54†	21	44†	NR
Gonadal steroid	Estrogen		Serious adverse events	IG1	12	21	2 (9.5)	21	1 (4.8)	NR
Gonadal steroid	Testosterone	Lu, 2006[246] Fair	Withdrawals due to adverse events	IG1	6	9	2 (22.2)	9	0 (0.0)	NR
Gonadal steroid	Estrogen	Mulnard, 2000[247] Fair	Withdrawals due to adverse events	IG1	12	42	7 (16.7)	39	2 (5.1)	NR
Gonadal steroid	Estrogen		Withdrawals due to adverse events	IG2	12	39	4 (10.3)	39	2 (5.1)	NR
Gonadal steroid	Estrogen plus progestin	Valen-Sendstad, 2010[248] Fair	Adverse events	IG1	12	33	25 (75.8)	32	18 (56.3)	NR
Gonadal steroid	Estrogen plus progestin		Serious adverse events	IG1	12	33	0 (0)	32	3 (9.4)	NR
Dietary supplement	B vitamins (including folic acid)	Aisen, 2008[250] Good	Adverse events	IG1	18	240	224 (93.3)	169	161 (95.3)	NR, 0.52
Dietary supplement	B vitamins (including folic acid)	Aisen, 2008[250] Good	Serious adverse events	IG1	18	240	123 (51.3)	169	95 (56.2)	NR, 0.37

Appendix F Table 5. Other Medications and Supplements: Detailed Results for Harms, by Medication Type

Medication type	Intervention	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
Dietary supplement	B vitamins (including folic acid)	de Jager, 2012[252] Fair	Adverse events	IG1	24	133	242†	133	271†	NR
Dietary supplement	Vitamin E	Dysken, 2014*[222] Good	Adverse events	IG2	48	152	198†	152	202†	NR
Dietary supplement	Vitamin E		Serious adverse events	IG2	48	152	180†	152	170†	NR
Dietary supplement	Vitamin E	Petersen, 2005[194] Fair	Adverse events	IG2	36	257	82†	259	64†	NR
Dietary supplement	Omega-3 fatty acids	Quinn, 2010[256] Fair	Adverse events	IG1	18	238	214†	164	144†	NR, 0.52
Dietary supplement	Omega-3 fatty acids		Serious adverse events	IG1	18	238	76†	164	50†	NR, 0.83
Dietary supplement	Omega-3 fatty acids		Withdrawals due to adverse events	IG1	18	238	14 (5.9)	164	10 (6.1)	NR
Dietary supplement	Omega-3 fatty acids	Shinto, 2014*[258] Fair	Adverse events	IG1	12	13	4†	13	7†	NR
Dietary supplement	Omega-3 and LA		Adverse events	IG2	12	13	7†	13	7†	NR
Dietary supplement	Omega-3 fatty acids - DHA	Sinn, 2012[259] Fair	Withdrawals due to adverse events	IG1	6	18	1 (5.6)	15	0 (0.0)	NR
Dietary supplement	Omega-3 fatty acids - EPA		Withdrawals due to adverse events	IG2	6	17	0 (0.0)	15	0 (0.0)	NR
Dietary supplement	Multivitamin	Sun, 2007[260] Fair	Adverse events	IG1	6	45	21 (46.7)	44	14 (31.8)	NR
Dietary supplement	Multivitamin		Serious adverse events	IG1	6	45	2 (4.4)	44	1 (2.3)	NR
Dietary supplement	Multivitamin	Sun, 2007[260] Fair	Withdrawals due to adverse events	IG1	6	45	5 (11.1)	44	4 (9.1)	NR

Appendix F Table 5. Other Medications and Supplements: Detailed Results for Harms, by Medication Type

Medication type	Intervention	Author, year Quality	Outcome	Int arm	Time, mo.	IG n at FU	IG FU N (%) with event	CG n at FU	CG FU N (%) with event	Between group difference, p-value
Dietary supplement	Omega-3 fatty acids	Yurko-Mauro, 2010[261] Good	Adverse events	IG1	6	242	109†	243	109†	NR
Dietary supplement	Omega-3 fatty acids		Serious adverse events	IG1	6	242	7 (2.9)	243	7 (2.9)	NR
Dietary supplement	Omega-3 fatty acids		Withdrawals due to adverse events	IG1	6	242	8 (3.3)	243	6 (2.5)	NR

* New study
† Number of events reported

Abbreviations: CG = control group; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FU = followup; HMG-CoA = β-Hydroxy β-methylglutaryl-CoA; IG = intervention group; Int arm = intervention arm; LA = linoleic acid; mo. = months; n (%) = number (percentage) of participants reporting events; NR = not reported; NSAID = Nonsteroidal Anti-inflammatory Drug

Appendix G Table 1. Patient-Level Nonpharmacologic Interventions: Detailed Results for Global Cognitive Function Outcomes, by Intervention Type

Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Cognitive Stimulation, Training, and Rehabilitation													
Amieva, 2016*[275] Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	NR	151	21.26 (12.9)	NR	NR	141	19.84 (11.5)	NR	NR, 0.5041
	Dem	ADAS-Cog 11 (0-70)	IG1	24	NR	124	39.96 (24.8)	NR	NR	109	38.25 (24.5)	NR	NR, 0.7060
	Dem	ADAS-Cog 11 (0-70)	IG2	3	NR	144	19.92 (12.0)	NR	NR	141	19.84 (11.5)	NR	NR, 0.8876
	Dem	ADAS-Cog 11 (0-70)	IG2	24	NR	121	34.57 (23.7)	NR	NR	109	38.25 (24.5)	NR	NR, 0.1012
Bergamaschi, 2013*[280] Fair	Dem	MMSE (0-30)	IG1	12	20.25 (2.95)	16	23.0 (2.0)	NR	21.94 (2.01)	16	18.37 (2.96)	NR	NR, <0.001
Buschert, 2011[269] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	6	12.1 (5.3)	8	11.4 (6.0)	NR	16.4 (4.8)	7	16.4 (4.9)	NR	NS
	MCI	ADAS-Cog 11 (0-70)	IG1	6	8.7 (2.9)	10	7.3 (3.1)	NR	9.8 (4.3)	12	11.7 (5.6)	NR	NR, 0.02
	Dem	MMSE (0-30)	IG1	6	24.5 (1.6)	8	25.0 (2.7)	NR	25.3 (1.5)	7	24.4 (2.4)	NR	NS
	MCI	MMSE (0-30)	IG1	6	28.1 (1.5)	10	26.8 (1.5)	NR	28.2 (1.2)	12	26.0 (1.3)	NR	NR, 0.07
Cavallo, 2016*[284] Good	Dem	MMSE (0-30)	IG1	6	22.65 (1.74)	38	22.32 (0.97)	NR	23.05 (2.44)	38	22.64 (0.96)	NR	NS
Chapman, 2004[266] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	4	NR	26	21.5 (NR)	NR	NR	28	20.2 (NR)	NR	NR
	Dem	ADAS-Cog 11 (0-70)	IG1	7	NR	26	23.5 (NR)	NR	NR	28	23.0 (NR)	NR	NR
	Dem	ADAS-Cog 11 (0-70)	IG1	12	NR	26	24.6	4.89 (2.67, 7.11)		28	26.5	5.62 (3.39, 7.85)	ES=0.00, NS
Chapman, 2004[266] Fair	Dem	MMSE (0-30)	IG1	4	NR	26	21.0 (NR)	NR	NR	28	21.9 (NR)	NR	NR
	Dem	MMSE (0-30)	IG1	7	NR	26	19.7 (NR)	NR	NR	28	20.1 (NR)	NR	NR
	Dem	MMSE (0-30)	IG1	12	NR	26	19.4 (NR)	-1.25 (-2.78, 0.28)	NR	28	19.0 (NR)	-2.14 (-4.18, -0.10)	ES=0.06, NS
Cove, 2014*[277] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	3	18.35 (7.1)	21	20.10 (7.6)	NR	17.68 (6.51)	23	20.09 (7.2)	NR	NS
	Dem	ADAS-Cog 11 (0-70)	IG2	3	18.13 (8.24)	24	19.04 (8.13)	NR	17.68 (6.51)	23	20.09 (7.2)	NR	NS

Appendix G Table 1. Patient-Level Nonpharmacologic Interventions: Detailed Results for Global Cognitive Function Outcomes, by Intervention Type

Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Dem	MMSE (0-30)	IG1	3	22.33 (3.54)	21	22.19 (4.48)	NR	22.91 (3.01)	23	22.13 (3.40)	NR	ES=0.003, 0.92
	Dem	MMSE (0-30)	IG2	3	22.71 (3.76)	24	22.38 (4.75)	NR	22.91 (3.01)	23	22.13 (3.40)	NR	NS
Fiatarone Singh, 2014*[278] Fair	MCI	ADAS-Cog 11 (0-70)	IG2	6	8.79 (NR)	24	7.31 (NR)	NR	8.09 (NR)	27	7.14 (NR)	NR	NR
	MCI	ADAS-Cog 11 (0-70)	IG2	18	8.79 (NR)	24	6.49 (NR)	NR	8.09 (NR)	27	5.75 (NR)	NR	NR
Greenaway, 2012[271] Fair	MCI	MMSE (0-30)	IG1	6	26.4 (2.2)	18	26.1 (2.2)	-0.2 (1.4)	27.2 (2.4)	17	27.3 (1.8)	-0.4 (2.2)	Cohen's d=0.1, NS
Jelcic, 2012*[282] Fair	Dem	MMSE (0-30)	IG1	3	24.4 (2.8)	20	26.4 (2.3)	NR	25.0 (2.6)	20	24.0 (3.3)	NR	NR, <0.001
Jeong, 2016*[274] Fair	MCI	ADAS-Cog 13 (0-89)	IG1	3	25.9 (6.6)	71	NR	-2.3 (4.6)	26.5 (6.6)	76	NR	-0.8 (4.8)	NR, 0.01
	MCI	ADAS-Cog 13 (0-89)	IG1	9	25.9 (6.6)	67	NR	-2.3 (5.2)	26.5 (6.6)	62	NR	-0.5 (5.2)	NR, 0.03
Jeong, 2016*[274] Fair	MCI	ADAS-Cog 13 (0-89)	IG2	3	24.9 (6.8)	71	NR	-2.5 (4.5)	26.5 (6.6)	76	NR	-0.8 (4.8)	NR, 0.02
	MCI	ADAS-Cog 13 (0-89)	IG2	9	24.9 (6.8)	68	NR	-2.3 (6.1)	26.5 (6.6)	62	NR	-0.5 (5.2)	NR, 0.047
	MCI	MMSE (0-30)	IG1	3	25.9 (2.5)	71	NR	0.3 (1.8)	25.3 (2.5)	76	NR	0.3 (1.8)	NR, 0.23
	MCI	MMSE (0-30)	IG1	9	25.9 (2.5)	67	NR	-0.1 (2.3)	25.3 (2.5)	62	NR	0.3 (2.4)	NR, 0.39
	MCI	MMSE (0-30)	IG2	3	25.9 (2.4)	77	NR	0.7 (2.0)	25.3 (2.5)	76	NR	0.3 (1.8)	NR, 0.16
	MCI	MMSE (0-30)	IG2	9	25.9 (2.4)	68	NR	0.2 (2.3)	25.3 (2.5)	62	NR	0.3 (2.4)	NR, 0.6
Kallio, 2018*[288] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	9	21.1 (8.1)	76	NR	0.8 (-0.2, 1.8)	21.8 (8.3)	71	NR	1.7 (0.6, 2.7)	NR, 0.23
	Dem	ADAS-Cog 11 (0-70)	IG1	9	21.1 (8.1)	76	NR	2.0 (0.9, 3.1)	21.8 (8.3)	71	NR	2.3 (1.1, 3.5)	NR, 0.43
Kurz, 2012[272] Fair	Dem	MMSE (0-30)	IG1	9	25.01 (2.16)	83	NR	-1.48 (3.77)	25.11 (2.20)	88	NR	-2.22 (3.24)	NR, 0.175
Olazaran, 2004[265] Fair	MCI + Dem	ADAS-Cog 11 (0-70)	IG1	3	24.7 (1.5)‡	40	NR	0 (NR)	25.8 (1.6)‡	40	NR	0.5 (NR)	NS
	MCI + Dem	ADAS-Cog 11 (0-70)	IG1	6	24.7 (1.5)‡	40	NR	0 (NR)	25.8 (1.6)‡	40	NR	2 (NR)	NS
Olazaran, 2004[265] Fair	MCI + Dem	ADAS-Cog 11 (0-70)	IG1	12	24.7 (1.5)‡	40	NR	4 (NR)	25.8 (1.6)‡	40	NR	6.5 (NR)	NS
	MCI + Dem	MMSE (0-30)	IG1	3	NR	40	NR	0 (NR)	NR	40	NR	-0.51 (NR)	NS
	MCI + Dem	MMSE (0-30)	IG1	6	NR	40	NR	-0.5 (NR)	NR	40	NR	-1.5 (NR)	NS

Appendix G Table 1. Patient-Level Nonpharmacologic Interventions: Detailed Results for Global Cognitive Function Outcomes, by Intervention Type

Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	MCI + Dem	MMSE (0-30)	IG1	12	NR	40	NR	-1.5 (NR)	NR	40	NR	-2.1 (NR)	NS
Orrell, 2014*[279] Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	31.1 (14.6)	123	35.32 (2.56)‡	NR	33.2 (13.0)	113	34.47 (2.59)‡	NR	Adj MD (95% CI)=-0.85 (-3.40, 1.70), 0.27
	Dem	ADAS-Cog 11 (0-70)	IG1	6	31.1 (14.6)	123	35.94 (2.79)‡	NR	33.2 (13.0)	113	35.29 (2.85)‡	NR	Adj MD (95% CI)=-0.65 (-3.71, 2.42), 0.67
	Dem	MMSE (0-30)	IG1	3	17.8 (5.6)	123	16.09 (0.88)‡	NR	17.8 (5.4)	113	15.79 (0.91)‡	NR	Adj MD (95% CI)=-0.30 (-0.72, 1.31), 0.56
	Dem	MMSE (0-30)	IG1	6	17.8 (5.6)	123	16.34 (1.21)‡	NR	17.8 (5.4)	113	15.49 (1.25)‡	NR	Adj MD (95% CI)=0.85 (-0.29, 1.99), 0.15
Orrell, 2017*[273] Good	Dem	ADAS-Cog 11 (0-70)	IG1	3	21.47 (9.22)	142	20.86 (9.73)	-0.29 (5.87)	19.79 (8.03)	146	19.50 (8.97)	0.03 (6.16)	Adj MD (95% CI)=0.29 (-1.10, 1.68), 0.68
	Dem	ADAS-Cog 11 (0-70)	IG1	6	21.47 (9.22)	134	20.69 (9.39)	0.33 (5.65)	19.79 (8.03)	139	20.39 (9.91)	1.24 (5.94)	Adj MD (95% CI)=-0.55 (-2.00, 0.90), 0.45
	Dem	MMSE (0-30)	IG1	3	21.12 (4.48)	142	20.59 (5.02)	-0.46 (3.18)	21.33 (4.11)	146	20.89 (4.83)	-0.87 (3.5)	Adj MD (95% CI)=0.16 (-0.60, 0.92), 0.69
Orrell, 2017*[273] Good	Dem	MMSE (0-30)	IG1	6	21.12 (4.48)	134	20.68 (4.76)	-0.96 (2.99)	21.33 (4.11)	139	21.19 (5.21)	-0.67 (3.62)	Adj MD (95% CI)=-0.47 (-1.26, 0.30), 0.23
Pantoni, 2017*[287] Fair	MCI	MMSE (0-30)	IG1	6	27.1 (2.6)	21	NR	-0.3 (1.9)	25.7 (3.2)	22	NR	-0.8 (1.9)	NR, 0.458
	MCI	MMSE (0-30)	IG1	12	27.1 (2.6)	21	NR	-0.7 (2.8)	25.7 (3.2)	22	NR	-0.3 (1.8)	NR, 0.601
	MCI	MMSE (0-30)‖	IG1	6	NA	21	20 (95.2)§	NA	NA	22	22 (100.0)§	NA	NR, 0.300
	MCI	MMSE (0-30)‖	IG1	12	NA	21	20 (95.2)§	NA	NA	22	21 (95.4)§	NA	NR, 0.973
Quayhagen, 1995[270] Fair	Dem	MDRS (0-144)	IG1	3	109.8 (12.0)	25	113.1 (11.7)	NR	109.2 (11.7)	25	104.8 (13.9)	NR	NR
	Dem	MDRS (0-144)	IG1	9	109.8 (12.0)	25	107.6 (15.1)	NR	109.2 (11.7)	25	96.6 (20.2)	NR	NR
Tsantali, 2017*[283] Fair	Dem	MMSE (0-30)	IG1	12	23.2 (1.6)	17	27.0 (1.0)	NR	23.1 (1.4)	21	21.6 (1.6)	NR	NR, <0.05
	Dem	MMSE (0-30)	IG2	12	22.5 (0.9)	17	20.9 (1.0)	NR	23.1 (1.4)	21	21.6 (1.6)	NR	NS

Appendix G Table 1. Patient-Level Nonpharmacologic Interventions: Detailed Results for Global Cognitive Function Outcomes, by Intervention Type

Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Tsolaki, 2011[263] Fair	MCI	MMSE (0-30)	IG1	6	28.09 (1.59)	104	29.00 (6.18)	NR	27.59 (1.88)	72	27.06 (2.34)	NR	NR, 0.000
Vidovich, 2015*[276] Good	MCI	CAMCOG-R (0-105)	IG1	12	89.5 (6.9)	77	NR	1.0 (0.3, 1.8)	90.6 (6.4)	77	NR	1.1 (0.4, 1.9)	NR
	MCI	CAMCOG-R (0-105)	IG1	24	89.5 (6.9)	67	NR	-0.6 (-2.3, 1.0)	90.6 (6.4)	60	NR	0.8 (-0.8, 2.5)	NR, 0.276
	MCI	MMSE (0-30)	IG1	24	NR	67	9 (13.4)§	NR	NR	60	2 (3.3)§	NR	OR (95% CI)=3.48 (0.92, 13.18), NS¶
Exercise Interventions													
Doi, 2017*[304] Good	MCI	MMSE (0-30)	IG1	9	26.0 (2.6)	55	NR	0.29 (2.6)	25.8 (2.4)	63	NR	-0.36 (2.3)	NR, 0.026
Hoffmann, 2016*[302] Good	Dem	MMSE (0-30)	IG1	4	23.8 (3.4)	102	23.9 (3.4)	NR	24.1 (3.8)	88	23.9 (3.9)	NR	MDC (95% CI)=0.5 (0.3, 1.2) 0.244
Holthoff, 2015*[303] Fair	Dem	MMSE (0-30)	IG1	3	22.05 (0.54)‡	15	21.99 (0.54)‡	NR	21.95 (0.54)‡	15	21.28 (0.54)‡	NR	Adj MD (95% CI)=0.70 (-0.83, 2.23) NR
	Dem	MMSE (0-30)	IG1	6	22.05 (0.54)‡	13	22.11 (0.57)‡	NR	21.95 (0.54)‡	14	20.72 (0.55)‡	NR	Adj MD (95% CI)=1.39 (-0.21, 2.98) NS
Hong, 2017*[300] Fair	MCI	MoCA (0-30)	IG1	3	20.70 (3.46)	10	21.70 (3.05)	NR	20.08 (4.44)	12	20.50 (5.05)	NR	NR, p=0.506
Lamb, 2018*[306] Good	Dem	ADAS-Cog 11 (0-70)	IG1	6	21.4 (9.6)	298	22.9 (11.6)	NR	21.8 (7.7)	145	22.4 (9.4)	NR	Adj MD (95% CI)= -0.6 (-1.58, 0.39), 0.237
	Dem	ADAS-Cog 11 (0-70)	IG1	12	21.4 (9.6)	278	25.2 (12.3)	NR	21.8 (7.7)	137	23.8 (10.4)	NR	Adj MD (95% CI)= -1.4 (-2.6, -0.2), 0.03
Lam, 2011[293] Fair	MCI	ADAS-Cog 11 (0-70)	IG1	5	12.6 (5.1)	135	10.7 (5.5)	2.0 (3.9)	14.1 (5.7)	194	12.8 (6.1)	1.3 (3.8)	NR
	MCI	MMSE (0-30)	IG1	5	24.8 (3.1)	135	25.8 (3.1)	0.9 (2.3)	24.2 (2.9)	194	25.1 (3.6)	0.8 (2.7)	NR
Lautenschlager, 2008[292] Good	MCI	ADAS-Cog 11 (0-70)	IG1	6	NR	85	NR	-0.26 (-0.89, 0.54)	NR	85	NR	1.04 (0.32, 1.82)	NR
	MCI	ADAS-Cog 11 (0-70)	IG1	12	NR	85	NR	-0.55 (-1.15, 0.20)	NR	85	NR	0.04 (-0.66, 0.64)	NR
	MCI	ADAS-Cog 11 (0-70)	IG1	17	NR	85	NR	-0.73 (-1.27, 0.03)	NR	85	NR	-0.04 (-0.46, 0.88)	NR, 0.04

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Lazarou, 2017*[299] Fair	MCI	MMSE (0-30)	IG1	10	27.60 (2.19)	66	28.00 (2.39)	NR	26.88 (2.1)	63	25.65 (3.27)	NR	NR, 0.000
Liu-Ambrose, 2016*[291] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	6	11.7 (5.5)	35	NR	-1.61 (0.50)‡	10.2 (5.4)	35	NR	0.10 (0.53)‡	MDC (95% CI)=-1.71 (-3.15, -0.26), 0.02
	Dem	ADAS-Cog 11 (0-70)	IG1	12	11.7 (5.5)	35	NR	-1.14 (0.57)‡	10.2 (5.4)	35	NR	-0.51 (0.64)‡	MDC (95% CI)=-0.63 (-2.34, 1.07), 0.46
Pitkälä, 2013*[290] Good	Dem	MMSE (0-30)	IG1	12	18.5 (6.3)	51	NR	-1.23 (-2.33, -0.14)	17.7 (6.2)	51	NR	-1.08 (-2.17, 0.02)	NR, 0.74
	Dem	MMSE (0-30)	IG2	12	17.8 (6.6)	68	NR	-1.63 (-2.64, -0.61)	17.7 (6.2)	65	NR	-1.08 (-2.17, 0.02)	NR, 0.74
Siu, 2018*[309] Fair	MCI	MMSE (0-30)	IG1	4	25.46 (1.89)	80	26.74 (2.42)	1.38 (2.22)	24.61 (2.75)	80	24.70 (2.90)	0.11 (2.78)	Beta (95% CI)=1.33 (0.53, 2.13), 0.001
Suzuki, 2012[297] Fair	MCI	ADAS-Cog 11 (0-70)	IG1	6	6.3 (2.2)	24	NR	-1.2 (-2.1, -0.3)	6.8 (2.2)	23	NR	-0.1 (-1.0, 0.8)	NS
	MCI	MMSE (0-30)	IG1	6	26.8 (1.8)	25	NR	0.32 (-0.96, 1.60)	26.6 (1.6)	25	NR	-1.37 (-2.66, -0.07)	NR, <0.05
	MCI	MMSE (0-30)	IG1	12	26.8 (1.8)	25	NR	-0.47 (-1.75, 0.81)	26.6 (1.6)	25	NR	-0.44 (-1.74, 0.86)	F statistic=3.4, 0.04
Venturelli, 2010[295] Fair	MCI + Dem	MMSE (0-30)	IG1	3	22.3 (2.1)	12	23.0 (1.4)	NR	22.1 (1.7)	11	17.5 (2.1)	NR	NR, <0.05
Vreugdenhil, 2012[298] Fair	Dem	ADAS-Cog 11 (0-70)	IG1	4	22.7 (9.7)	20	18.5 (9.8)	-4.9 (1.1)‡	26.6 (16.6)	20	30.6 (17.9)	2.1 (1.4)‡	NR, 0.001
	Dem	MMSE (0-30)	IG1	4	22.9 (5.0)	20	23.9 (5.0)	1.0 (1.4)‡	21.0 (6.3)	20	19.0 (7.7)	-1.6 (0.5)‡	NR, 0.001
Multicomponent and Other Interventions													
Bae, 2019*[320] Fair	MCI	MMSE (0-30)	IG1	6	27.1 (2.1)	41	NR	0.51 (-1.35, 0.34)	26.7 (2.0)	42	NR	0.35 (-0.44, 1.15)	NR, 0.143
Burgener, 2008[312] Fair	Dem	MMSE (0-30)	IG1	5	24.8 (3.5)	19	25.2 (3.1)	0.4 (NR)	22.9 (5.2)	14	22.4 (7.6)	-0.5 (NR)	NR, 0.05
Fiatarone Singh, 2014*[278] Fair	MCI	ADAS-Cog 11 (0-70)	IG1	6	8.02 (NR)	27	6.26 (NR)	NR	8.09 (NR)	27	7.14 (NR)	NR	NR
	MCI	ADAS-Cog 11 (0-70)	IG1	18	8.02 (NR)	27	5.76 (NR)	NR	8.09 (NR)	27	5.75 (NR)	NR	NR
Jha, 2013*[316] Fair	MCI + Dem	MMSE (0-30)	IG1	6	21 (6)	17	21 (6)	-0.06 (NR)	23 (5)	17	22 (6)	0.7 (NR)	NR, 0.44

Appendix G Table 1. Patient-Level Nonpharmacologic Interventions: Detailed Results for Global Cognitive Function Outcomes, by Intervention Type

Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Marshall, 2015*[315] Fair	Dem	MMSE (0-30)	IG1	3	23.6 (4.3)	28	22.4 (4.0)	NR	22.4 (3.7)	27	22.9 (3.1)	NR	MDC (95% CI): -1.34 (-2.88, 0.20), NS
	Dem	MMSE (0-30)	IG1	5	23.6 (4.3)	28	22.5 (4.4)	NR	22.4 (3.7)	24	22.4 (2.9)	NR	MDC (95% CI): -0.45 (-2.07, 1.16), NS
Richard, 2009[317] Fair	Dem	MMSE (0-30)	IG1	12	22.3 (3.3)	57	19.7 (5.1)	NR	22.2 (3.6)	48	19.5 (5.2)	NR	NS
	Dem	MMSE (0-30)	IG1	24	22.3 (3.3)	50	16.8 (8.1)	-5.78 (6.4)	22.2 (3.6)	44	17.0 (6.4)	-5.23 (6.0)	MDC (95% CI): -0.55 (-3.12, 2.02), 0.65
Rovner, 2018*[318] Good	MCI	MMSE (0-30)	IG1	6	25.8 (2.3)	111	NR	0.01 (-0.39, 0.41)	25.6 (2.5)	110	NR	-0.22 (-0.59, 0.15)	ES (95% CI)=0.23 (-0.32, 0.77), 0.41
Shimada, 2017*[321] Fair	MCI	MMSE (0-30)	IG1	9	26.6 (1.8)	154	NR	0.0 (-0.4, 0.4)	26.8 (1.8)	154	NR	-0.8 (-1.2, -0.4)	MDC (95% CI)=0.8 (0.2, 1.4), 0.012
Straubmeier, 2017*[322] Fair	MCI + Dem	MMSE (0-30)	IG1	6	19.8 (4.8)	255	19.9 (6.0)	NR	19.3 (4.8)	178	18.3 (6.2)	NR	ES=0.21, 0.033
Train the Brain Consortium, 2017*[319] Fair	MCI	ADAS-Cog 11 (0-70)	IG1	7	NR	55	NR	-1.40 (0.32)‡	NR	58	NR	1.1526. (0.25)‡	MDC (95% CI)=-2.17 (-2.99, -1.34), <0.0001
	MCI	ADAS-Cog 11 (0-70)#	IG1	7	NA	55	25 (45.4)	NA	NA	58	7 (12.1)	NA	NR, <0.001
Wolfs, 2008[313] Fair	MCI + Dem	MMSE (0-30)	IG1	6	20.5 (6.0)	116	18.8 (7.8)	NR	19.8 (6.6)	83	19.2 (7.5)	NR	MDC (95% CI): -0.9 (-2.23, 0.34), NS
		MMSE (0-30)	IG1	12	20.5 (6.0)	113	18.0 (7.7)	NR	19.8 (6.6)	77	17.4 (8.8)	NR	MDC (95% CI): 0.0 (-1.43, 1.48), NS

* New study
† Higher scores indicate better outcomes for all instruments except for ADAS-Cog 11 and ADAS-Cog 13 where lower scores indicate better outcomes
‡ Standard error
§ N (%)
‖ Participants with stable/better MMSE scores at followup
¶ Odds of attaining a MMSE score <24
# Participants with decerase of 1.5 points on ADAS-Cog (improvement)

Abbreviations: ADAS-Cog 11 = Alzheimer's Disease Assessment Scale-cognitive subscale; 11-item; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-cognitive subscale; 13-item; Adj MD = adjusted mean difference; BL = baseline; CAMCOG-R = Cambridge Cognitive Examination Revised; CG = control group; CI = confidence interval; Dem = dementia; FU = followup; IG = intervention group; Int arm = intervention arm; MCI = mild cognitive impairment; MDC = mean difference in change; MDRS = Mattis Dementia

Appendix G Table 1. Patient-Level Nonpharmacologic Interventions: Detailed Results for Global Cognitive Function Outcomes, by Intervention Type

Rating Scale; MMSE = Mini-Mental State Examination; mo. = months; MoCA = Montreal Cognitive Assessment Test; Pop cat = population category; NR = not reported; NS = Not statistically significant; SD = standard deviation

Appendix G Table 2. Patient-Level Nonpharmacologic Interventions: Detailed Results for Physical Function Outcomes, by Intervention Type

Author, year Quality	Pop cat	ADL or IADL (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Cognitive Stimulation, Training, and Rehabilitation													
Amieva, 2016*[275] Good	Dem	ADL/IADL (DAD, 0-40, ↑)	IG1	3	26.5 (8.1)	151	27.54 (9.2)	NR	26.6 (8.8)	141	26.94 (9.6)	NR	NR, 0.6201
	Dem	ADL/IADL (DAD, 0-40, ↑)	IG1	24	26.5 (8.1)	124	24.74 (13.4)	NR	26.6 (8.8)	109	25.38 (13.4)	NR	NR, 0.6695
	Dem	ADL/IADL (DAD, 0-40, ↑)	IG2	3	26.5 (8.1)	144	28.19 (9.4)	NR	26.6 (8.8)	141	26.94 (9.6)	NR	NR,
	Dem	ADL/IADL (DAD, 0-40, ↑)	IG2	24	26.5 (8.1)	121	27.04 (11.9)	NR	26.6 (8.8)	109	25.38 (13.4)	NR	NR, 0.3882
Belleville, 2018*[289] Fair	MCI	ADL (ADL-PI, 0-45, ↓)	IG1	3	38.66 (4.95)	36	39.31 (4.39)	NR	37.70 (5.11)	38	38.24 (6.07)	NR	NS
	MCI	ADL (ADL-PI, 0-45, ↓)	IG1	6	38.66 (4.95)	31	39.28 (4.41)	NR	37.70 (5.11)	38	38.30 (5.67)	NR	NS
Bergamaschi, 2013*[280] Fair	Dem	ADL (Katz Index, 0-6, ↑)	IG1	12	5.06 (1.12)	16	4.75 (1.34)	NR	5.18 (1.18)	16	3.75 (1.75)	NR	NR, <0.05
	Dem	IADL (Lawton and Brody IADL, 0-8, ↑)	IG1	12	3.94 (2.51)	16	3.56 (2.34)	NR	3.94 (2.41)	16	2.62 (1.76)	NR	NS
Cahn-Weiner, 2003[267] Fair	Dem	ADL/IADL (Lawton and Brody IADL + Physical Self Maintenance Scale, NR, ↑)	IG1	3	18.8 (5.0)	15	19.4 (4.8)	NR	20.7 (4.8)	14	20.2 (5.7)	NR	NS
Chapman, 2004[266] Fair	Dem	ADL/IADL (TFLS, 0-52, ↓)	IG1	4	NR	26	30.5 (NR)	NR	NR	28	29.7 (NR)	NR	NR
	Dem	ADL/IADL (TFLS, 0-52, ↓)	IG1	7	NR	26	29.0 (NR)	NR	NR	28	28.7 (NR)	NR	NR
	Dem	ADL/IADL (TFLS, 0-52, ↓)	IG1	12	NR	26	28.5 (NR)	-2.89 (-5.66, -0.12)	NR	28	26.4 (NR)	-6.86 (NR) (-10.72, -3.00)	ES=0.12, NS
Fiatarone Singh, 2014*[278] Fair	MCI	IADL (B-ADL,1-10†, ↓)	IG2	6	0.3 (NR)	24	0.1 (NR)	NR	0.2 (NR)	27	0.1 (NR)	NR	NS
	MCI	IADL (B-ADL,1-10†, ↓)	IG2	18	0.3 (NR)	24	0.1 (NR)	NR	0.2 (NR)	27	0.1 (NR)	NR	NS
Hyer, 2016*[285] Fair	MCI	IADL (FAQ, 0-30, ↓)	IG1	5	1.72 (3.59)	34	1.33 (3.18)	NR	2.06 (2.49)	34	3.12 (4.53)	NR	NR, 0.04
Jelcic, 2012*[282] Fair	Dem	IADL (Lawton and Brody IADL, 0-8, ↑)	IG1	3	7.3 (1.7)	20	7.4 (1.6)	NR	6.6 (2.1)	20	6.6 (2.2)	NR	NS
Jeong, 2016*[274] Fair	MCI	IADL (B-ADL,1-10, ↓)	IG1	3	2.7 (1.3)	71	NR	-0.1 (1.2)	2.7 (1.3)	76	NR	-0.1 (0.8)	NR, 0.81

Appendix G Table 2. Patient-Level Nonpharmacologic Interventions: Detailed Results for Physical Function Outcomes, by Intervention Type

Author, year Quality	Pop cat	ADL or IADL (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	MCI	IADL (B-ADL,1-10, ↓)	IG1	9	2.7 (1.3)	67	NR	0.0 (1.1)	2.7 (1.3)	62	NR	0.2 (1.2)	NR, 0.22
	MCI	IADL (B-ADL,1-10, ↓)	IG2	3	2.5 (1.3)	77	NR	0.0 (1.0)	2.7 (1.3)	76	NR	-0.1 (0.8)	NR, 0.93
	MCI	IADL (B-ADL,1-10, ↓)	IG2	9	2.5 (1.3)	68	NR	0.2 (1.3)	2.7 (1.3)	62	NR	0.2 (1.2)	NR, 0.71
Kurz, 2012[272] Fair	Dem	IADL (B-ADL,1-10, ↓)	IG1	3	3.54 (1.88)	92	NR	0.13 (1.25)	3.67 (1.93)	97	NR	0.28 (1.53)	NR, 0.44
	Dem	IADL (B-ADL,1-10, ↓)	IG1	9	3.54 (1.88)	83	NR	0.73 (1.82)	3.67 (1.93)	88	NR	0.86 (1.59)	NR, 0.64
Olazaran, 2004[265] Fair	MCI + Dem	IADL (FAQ, 0-30, ↓)	IG1	3	15.3 (1.1)‡	40	NR	1.5 (NR)	14.1 (1.1)‡	40	NR	2 (NR)	NS
	MCI + Dem	IADL (FAQ, 0-30, ↓)	IG1	6	15.3 (1.1)‡	40	NR	2.1 (NR)	14.1 (1.1)‡	40	NR	4.6 (NR)	NS
	MCI + Dem	IADL (FAQ, 0-30, ↓)	IG1	12	15.3 (1.1)‡	40	NR	4.2 (NR)	14.1 (1.1)‡	40	NR	6 (NR)	NS
Orrell, 2014*[279] Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	3	42.7 (17.2)	123	43.58 (2.32)‡	NR	41.5 (18.1)	113	40.94 (2.32)‡	NR	Adj MD (95% CI)=2.64 (0.08, 5.20), 0.04
	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	42.7 (17.2)	123	43.29 (2.88)‡	NR	41.5 (18.1)	113	42.35 (2.87)‡	NR	Adj MD (95% CI)=0.94 (-2.04, 3.92), 0.54
Orrell, 2017*[273] Good	Dem	ADL/IADL (Bristol ADL, 0-60, ↓)	IG1	3	5.16 (5.45)	142	14.53 (10.34)	9.51 (6.23)	4.49 (4.09)	146	13.55 (8.20)	9.35 (5.91)	Adj MD (95% CI)=-0.20 (-1.44, 1.04), 0.75
	Dem	ADL/IADL (Bristol ADL, 0-60, ↓)	IG1	6	5.16 (5.45)	134	15.39 (10.78)	10.52 (6.97)	4.49 (4.09)	139	14.56 (8.86)	10.55 (6.54)	Adj MD (95% CI)=-0.66 (-2.07, 0.75), 0.36
Pantoni, 2017*[287] Fair	MCI	ADL (Katz Index, 0-6, ↑)	IG1	6	5.9 (0.3)	21	NR	0.1 (0.3)	5.9 (0.4)	22	NR	0 (0)	NR, 0.145
	MCI	ADL (Katz Index, 0-6, ↑)	IG1	12	5.9 (0.3)	21	NR	0 (0.9)	5.9 (0.4)	22	NR	-0.2 (0.7)	NR, 0.262
	MCI	ADL/IADL (DAD, 0-100, ↑)	IG1	6	91.9 (11.9)	21	NR	-2.2 (10.3)	84.2 (17.8)	22	NR	-3.9 (11.3)	NR, 0.612
	MCI	ADL/IADL (DAD, 0-100, ↑)	IG1	12	91.9 (11.9)	21	NR	-8.4 (21.1)	84.2 (17.8)	22	NR	-6.9 (17.2)	NR, 0.800

Appendix G Table 2. Patient-Level Nonpharmacologic Interventions: Detailed Results for Physical Function Outcomes, by Intervention Type

Author, year Quality	Pop cat	ADL or IADL (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	MCI	IADL (Lawton and Brody IADL, 0-8, ↑)	IG1	6	1.9 (2.1)	21	NR	-0.4 (1.1)	2.2 (2.4)	22	NR	0 (0.9)	NR, 0.240
	MCI	IADL (Lawton and Brody IADL, 0-8, ↑)	IG1	12	1.9 (2.1)	21	NR	-0.7 (1.1)	2.2 (2.4)	22	NR	-1 (1.7)	NR, 0.457
Tsolaki, 2011[263] Fair	MCI	ADL (FRSSD, NR, ↓)	IG1	6	3.04 (1.61)	104	2.67 (1.7)	NR	3.11 (1.68)	72	3.91 (2.49)	NR	NR, 0.001
Exercise Interventions													
Dawson, 2016*[305] Fair	Dem	ADL/IADL (ADL/IADL [unspecified], 0-48, ↓)	IG1	3	7.25 (5.13)	13	6.83 (5.13)	NR	4.20 (3.85)	10	5.40 (6.72)	NR	NR, 0.36
Ho, 2018*[308] Fair	MCI + Dem	IADL (Lawton and Brody IADL, 0-18, ↑)	IG1	3	12.8 (5.0)	69	13.2 (4.9)	NR	14.0 (4.9)	68	12.6 (5.9)	NR	Beta (SE)=1.92 (0.58), <0.01
	MCI + Dem	IADL (Lawton and Brody IADL, 0-18, ↑)	IG1	6	12.8 (5.0)	69	12.8 (5.0)	NR	14.0 (4.9)	68	11.7 (6.2)	NR	NS
	MCI + Dem	IADL (Lawton and Brody IADL, 0-18, ↑)	IG1	12	12.8 (5.0)	69	11.8 (6.0)	NR	14.0 (4.9)	68	11.4 (6.2)	NR	NS
	MCI + Dem	IADL (Lawton and Brody IADL, 0-18, ↑)	IG2	3	12.8 (5.2)	67	11.8 (5.4)	NR	14.0 (4.9)	68	12.6 (5.9)	NR	Beta (SE)=0.74 (0.59), 0.21
	MCI + Dem	IADL (Lawton and Brody IADL, 0-18, ↑)	IG2	6	12.8 (5.2)	67	11.1 (6.1)	NR	14.0 (4.9)	68	11.7 (6.2)	NR	NS
	MCI + Dem	IADL (Lawton and Brody IADL, 0-18, ↑)	IG2	12	12.8 (5.2)	67	10.4 (6.0)	NR	14.0 (4.9)	68	11.4 (6.2)	NR	NS
Hoffmann, 2016*[302] Good	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	4	64.8 (8.8)	102	64.4 (9.4)	NR	62.4 (10.8)	88	62.7 (10.4)	NR	MDC (95% CI)=-0.1 (-1.8, 1.5), 0.868
Holthoff, 2015*[303] Fair	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	3	60.55 (0.91)‡	15	62.35 (0.91)‡	NR	60.53 (0.91)‡	15	57.47 (0.91)‡	NR	Adj MD (95% CI)=4.89 (2.30, 7.48), NR
	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	60.55 (0.91)‡	13	61.26 (1.00)‡	NR	60.53 (0.91)‡	14	53.50 (0.94)‡	NR	Adj MD (95% CI)=7.76 (5.01, 10.51), <0.05
Liu-Ambrose, 2016*[291] Fair	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	6	46.1 (6.8)‡	35	NR	0.77 (0.65)‡	46.5 (5.1)‡	35	NR	0.49 (0.69)‡	MDC (95% CI)=1.25 (-0.63, 3.13), 0.19

Appendix G Table 2. Patient-Level Nonpharmacologic Interventions: Detailed Results for Physical Function Outcomes, by Intervention Type

Author, year Quality	Pop cat	ADL or IADL (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Dem	ADL/IADL (ADCS-ADL, 0-78, ↑)	IG1	12	46.1 (6.8)	35	NR	0.22 (0.70)‡	46.5 (5.1)	35	NR	-1.13 (0.73)‡	MDC (95% CI)=1.34 (-0.68, 3.37), 0.19
Morris, 2017*[301] Good	MCI + Dem	ADL/IADL (DAD, 0-100, ↑)	IG1	3	88.0 (12.3)	36	89.8 (12.5)	NR	91.2 (8.0)	37	89.5 (12.8)	NR	NR,
	MCI + Dem	ADL/IADL (DAD, 0-100, ↑)	IG1	6	88.0 (12.3)	34	89.5 (13.7)	NR	91.2 (8.0)	34	86.7 (13.3)	NR	ES (95% CI)=5.27 (1.7, 8.84), 0.02
Pitkälä, 2013*[290] Good	Dem	ADL/IADL (FIM, 18-126, ↑)	IG1	3	88.5 (19.0)	61	NR	-5.52 (-7.21, -3.73)	86.8 (17.9)	65	NR	-6.17 (-7.93, -4.56)	NR
	Dem	ADL/IADL (FIM, 18-126, ↑)	IG1	6	88.5 (19.0)	61	NR	-8.9 (-11.2, -6.7)	86.8 (17.9)	65	NR	-11.8 (-14.0, -9.7)	NR, 0.07
	Dem	ADL/IADL (FIM, 18-126, ↑)	IG1	12	88.5 (19.0)	61	NR	-10.3 (-13.9, -6.7)	86.8 (17.9)	65	NR	-14.4 (-18.0, -10.9)	NR, 0.12
	Dem	ADL/IADL (FIM, 18-126, ↑)	IG2	3	87.3 (19.1)	68	NR	-5.0 (-6.77, -3.44)	86.8 (17.9)	65	NR	-6.17 (-7.93, -4.56)	NR
	Dem	ADL/IADL (FIM, 18-126, ↑)	IG2	6	87.3 (19.1)	68	NR	-6.5 (-8.6, -4.4)	86.8 (17.9)	65	NR	-11.8 (-14.0, -9.7)	NR, 0.001
	Dem	ADL/IADL (FIM, 18-126, ↑)	IG2	12	87.3 (19.1)	68	NR	-7.1 (-10.5, -3.7)	86.8 (17.9)	65	NR	-14.4 (-18.0, -10.9)	NR, 0.004
Venturelli, 2010[295] Fair	MCI + Dem	ADL (Barthel Index, 0-100, ↑)	IG1	3	19.6 (12.8)	12	34.8 (14.9)	NR	19.6 (11.3)	11	19.3 (11.9)	NR	NR, <0.05
Vreugdenhil, 2012[298] Fair	Dem	ADL (Barthel Index, 0-100, ↑)	IG1	4	10.6 (4.1)	20	11.0 (4.1)	0.5 (0.3)‡	8.6 (4.2)	20	7.6 (4.5)	-1.1 (0.4)‡	NR, 0.047
	Dem	IADL (Lawton and Brody IADL, 0-14, ↑)	IG1	4	99.5 (1.5)	20	99.6 (1.2)	-0.4 (0.8)‡	98.4 (5.4)	20	94.2 (12.6)	-3.0 (0.9)‡	NR, 0.007
Multicomponent and Other Interventions													
Belleville, 2018*[289] Fair	MCI	ADL (ADL-PI, 0-45, ↓)	IG2	3	39.63 (5.53)	40	40.24 (4.69)	NR	37.70 (5.11)	38	38.24 (6.07)	NR	NS
	MCI	ADL (ADL-PI, 0-45, ↓)	IG2	6	39.63 (5.53)	31	38.91 (6.66)	NR	37.70 (5.11)	38	38.30 (5.67)	NR	NS
Fiatarone Singh, 2014*[278] Fair	MCI	IADL (B-ADL,1-10†, ↓)	IG1	6	0.2 (NR)	27	0.2 (NR)	NR	0.2 (NR)	27	0.1 (NR)	NR	NS
	MCI	IADL (B-ADL,1-10†, ↓)	IG1	18	0.2 (NR)	27	0.2 (NR)	NR	0.2 (NR)	27	0.1 (NR)	NR	NS
Richard, 2009[317] Fair	Dem	ADL/IADL (IDDD - performance scale, 0-44, ↓)	IG1	12	9.5 (9.4)	57	10.9 (7.4)	NR	10.7 (9.3)	48	15.2 (10.9)	NR	NS

Appendix G Table 2. Patient-Level Nonpharmacologic Interventions: Detailed Results for Physical Function Outcomes, by Intervention Type

Author, year Quality	Pop cat	ADL or IADL (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Dem	ADL/IADL (IDDD - performance scale, 0-44, ↓)	IG1	24	9.5 (9.4)	50	17.9 (13.5)	13.75 (10.3)	10.7 (9.3)	44	22.8 (13.4)	11.04 (13.1)	MDC (95% CI)=2.71 (-3.14, 8.56), 0.26
Straubmeier, 2017*[322] Fair	MCI + Dem	ADL (Erlangen Test of ADL, 0-30, ↑)	IG1	6	17.9 (6.9)	255	18.2 (7.0)	NR	17.1 (7.5)	178	16.4 (8.4)	NR	ES=0.20, 0.019
Wolfs, 2008[313] Fair	MCI + Dem	IADL (Lawton and Brody IADL, 0-14, ↑)	IG1	6	17.1 (5.7)	116	18.7 (6.2)	NR	16.5 (6.1)	83	18.1 (6.3)	NR	MDC (95% CI) = -0.1 (-1.16, 1.06), NS
	MCI + Dem	IADL (Lawton and Brody IADL, 0-14, ↑)	IG1	12	17.1 (5.7)	113	20.2 (6.1)	NR	16.5 (6.1)	77	20.4 (6.5)	NR	MDC (95% CI) = -0.7 (-1.85, 0.46), NS

* New study
† Scale was logged prior to analysis
‡ Standard error

Abbreviations: ADL = Activities of Daily Living; ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living 23 items; Adj MD = adjusted mean difference; B-ADL = Bayer Activities of Daily Living; Barthel Index = Barthel Index Activities of Daily Living; BL = baseline; Bristol ADL = Bristol Activities of Daily Living Scale; CG = control group; CI = confidence interval; DAD = Disability Assessment for Dementia; Dem = dementia; FAQ = Functional Activities Questionnaire; FIM = Functional Independence Measure; FRSSD = Functional Rating Scale for the Symptoms of Dementia; FU = followup; IADL = Instrumental Activities of Daily Living; IDDD = Interview for Deterioration in Daily Living Activities in Dementia; IG = intervention group; Int arm = intervention arm; Katz Index = Katz Index of Independence in Activities of Daily Living; MCI = mild cognitive impairment; MDC = mean difference in change; mo. = months; Pop cat = population category; NR = not reported; NS = Not statistically significant; SD = standard deviation; TFLS = Texas Functional Living Scale

Appendix G Table 3. Patient-Level Nonpharmacologic Interventions: Detailed Results for Quality of Life Outcomes, by Intervention Type

Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Cognitive Stimulation, Training, and Rehabilitation													
Amieva, 2016*[275] Good	Dem	QOL-AD (13-52)	IG1	3	NR	151	31.99 (8.0)	NR	NR	141	33.28 (7.7)	NR	NR, 0.2161
	Dem	QOL-AD (13-52)	IG1	24	NR	124	27.39 (9.2)	NR	NR	109	28.83 (9.5)	NR	NR, 0.1304
	Dem	QOL-AD (13-52)	IG2	3	NR	144	32.97 (7.7)	NR	NR	141	33.28 (7.7)	NR	NR, 0.7987
	Dem	QOL-AD (13-52)	IG2	24	NR	121	29.05 (9.2)	NR	NR	109	28.83 (9.5)	NR	NR, 0.9413
Buschert, 2011[269] Fair	Dem	QOL-AD (13-52)	IG1	6	39.1 (7.4)	8	38.7 (7.6)	NR	33.5 (4.0)	7	32.6 (3.8)	NR	NS
	MCI	QOL-AD (13-52)	IG1	6	35.3 (3.8)	10	35.7 (5.1)	NR	36.6 (5.0)	12	34.7 (5.5)	NR	NS
Chapman, 2004[266] Fair	Dem	QOL-AD (0-52)‡	IG1	4	NR	26	35.2 (NR)	NR	NR	28	36.2 (NR)	NR	NR
	Dem	QOL-AD (0-52)‡	IG1	7	NR	26	36.0 (NR)	NR	NR	28	35.0 (NR)	NR	NR
	Dem	QOL-AD (0-52)‡	IG1	12	NR	26	35.8 (NR)	1.05 (-1.32, 3.42)	NR	28	36.0 (NR)	1.33 (-0.51, 3.17)	ES=0.02, NS
	Dem	QOL-AD (0-52)§	IG1	4	NR	26	37.6 (NR)	NR	NR	28	37.1 (NR)	NR	NR
	Dem	QOL-AD (0-52)§	IG1	7	NR	26	38.4 (NR)	NR	NR	28	36.9 (NR)	NR	NR
	Dem	QOL-AD (0-52)§	IG1	12	NR	26	38.5 (NR)	1.77 (-0.38, 3.92)	NR	28	37.2 (NR)	0.38 (-1.14, 1.90)	ES=0.26, NS
	Dem	QOL-AD (13-52)	IG1	4	NR	26	38.7 (NR)	NR	NR	28	37.6 (NR)	NR	NR
Chapman, 2004[266] Fair	Dem	QOL-AD (13-52)	IG1	7	NR	26	39.5 (NR)	NR	NR	28	37.9 (NR)	NR	NR
	Dem	QOL-AD (13-52)	IG1	12	NR	26	39.9 (NR)	2.05 (-0.25, 4.35)	NR	28	37.9 (NR)	-0.10 (-2.43, 2.23)	ES=0.33 , NR, NS
Cove, 2014*[277] Fair	Dem	QOL-AD (13-52)	IG1	3	36.43 (6.06)	21	36.45 (5.6)	NR	34.78 (5.43)	23	35.32 (5.51)	NR	NS
	Dem	QOL-AD (13-52)	IG2	3	36.42 (5.44)	24	35.65 (5.83)	NR	34.78 (5.43)	23	35.32 (5.51)	NR	NS
Greenaway, 2012[271] Fair	MCI	QOL-AD (13-52)	IG1	6	43.4 (6.0)	18	43.8 (6.2)	0.6 (2.4)	43.0 (5.1)	17	43.5 (4.0)	-0.6 (3.1)	Cohen's d=0.41, NS
Jeong, 2016*[274] Fair	MCI	QOL-AD (0-52)	IG1	3	NR	71	NR	1.1 (4.2)	NR	76	NR	-0.3 (4.1)	NR, 0.05
	MCI	QOL-AD (0-52)	IG1	9	NR	67	NR	0.7 (3.6)	NR	62	NR	-0.1 (4.7)	NR, 0.13
	MCI	QOL-AD (13-52)	IG2	3	NR	77	NR	0.9 (2.9)	NR	76	NR	-0.3 (4.1)	NR, 0.01
	MCI	QOL-AD (13-52)	IG2	9	NR	68	NR	0.7 (3.3)	NR	62	NR	-0.1 (4.7)	NR, 0.04
Kallio, 2018*[288] Fair	Dem	15D Index value (0-1)	IG1	3	0.740 (0.086)	76	NR	-0.040 (-0.058, -0.021)	0.741 (0.083)	71	NR	-0.037 (-0.056, -0.018)	NR, 0.82

Appendix G Table 3. Patient-Level Nonpharmacologic Interventions: Detailed Results for Quality of Life Outcomes, by Intervention Type

Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Dem	15D Index value (0-1)	IG1	9	0.740 (0.086)	76	NR	-0.048 (-0.065, -0.031)	0.741 (0.083)	71	NR	-0.058 (-0.077, -0.038)	NR, 0.61
Kurz, 2012[272] Fair	Dem	DEMQOL (28-112)‡	IG1	3	94.3 (14.6)	92	NR	-1.10 (10.40)	89.9 (15.4)	97	NR	-2.06 (13.08)	NR, 0.58
	Dem	DEMQOL (28-112)‡	IG1	9	94.3 (14.6)	83	NR	-2.75 (11.47)	89.9 (15.4)	88	NR	-4.89 (13.65)	NR, 0.28
	Dem	DEMQOL (28-112)	IG1	3	91.3 (12.4)	92	NR	0.52 (9.79)	87.5 (13.8)	97	NR	-0.03 (12.02)	NR, 0.73
	Dem	DEMQOL (28-112)	IG1	9	91.3 (12.4)	83	NR	0.67 (9.56)	87.5 (13.8)	88	NR	-2.32 (13.05)	NR, 0.09
Orrell, 2014*[279] Good	Dem	DEMQOL (28-112)‡	IG1	3	102.2 (13.5)	123	101.36 (2.67)‖	NR	102.2 (11.2)	113	98.12 (2.67)‖	NR	Adj MD (95% CI)=3.24 (0.29, 6.19), 0.03
Orrell, 2014*[279] Good	Dem	DEMQOL (28-112)‡	IG1	6	102.2 (13.5)	123	97.75 (3.23)‖	NR	102.2 (11.2)	113	96.61 (3.21)‖	NR	Adj MD (95% CI)=1.13 (-2.24, 4.51), 0.50
	Dem	DEMQOL (28-112)	IG1	3	94.8 (10.9)	123	89.85 (2.34)‖	NR	95.1 (11.7)	113	90.71 (2.38)‖	NR	Adj MD (95% CI)=-0.86 (-3.45, 1.73), 0.54
	Dem	DEMQOL (28-112)	IG1	6	94.8 (10.9)	123	89.13 (3.55)‖	NR	95.1 (11.7)	113	88.83 (3.56)‖	NR	Adj MD (95% CI)=0.30 (-2.70, 3.31), 0.87
	Dem	QOL-AD (13-52)‡	IG1	3	33.7 (5.9)	123	33.93 (1.05)‖	NR	33.3 (4.9)	113	32.40 (1.07)‖	NR	Adj MD (95% CI)=1.53 (0.37, 2.69), 0.01
	Dem	QOL-AD (13-52)‡	IG1	6	33.7 (5.9)	123	34.12 (1.41)‖	NR	33.3 (4.9)	113	34.05 (1.41)‖	NR	Adj MD (95% CI)=0.07 (-1.39, 1.53), 0.95
	Dem	QOL-AD (13-52)	IG1	3	36.1 (4.8)	123	34.29 (1.03)‖	NR	36.5 (5.7)	113	33.97 (1.04)‖	NR	Adj MD (95% CI)=0.32 (-0.88, 1.52), 0.54

Appendix G Table 3. Patient-Level Nonpharmacologic Interventions: Detailed Results for Quality of Life Outcomes, by Intervention Type

Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Dem	QOL-AD (13-52)	IG1	6	36.1 (4.8)	123	35.62 (1.43)‖	NR	36.5 (5.7)	113	33.84 (1.53)‖	NR	Adj MD (95% CI)=1.78 (-0.01, 3.57), 0.03
Orrell, 2017*[273] Good	Dem	DEMQOL single item (1-4)‡	IG1	3	93.85 (11.76)	142	94.08 (10.92)	-0.47 (7.59)	92.18 (13.55)	146	94.05 (11.80)	0.32 (10.85)	Adj MD (95% CI)=-0.33 (-2.31, 1.65), 0.74
Orrell, 2017*[273] Good	Dem	DEMQOL single item (1-4)‡	IG1	6	93.85 (11.76)	134	95.46 (11.17)	1.09 (7.2)	92.18 (13.55)	139	95.12 (11.11)	1.56 (10.39)	Adj MD (95% CI)=0.31 (-1.62, 2.22), 0.79
	Dem	QOL-AD (13-52)‡	IG1	3	38.01 (5.44)	142	37.90 (5.52)	-0.36 (5.01)	37.96 (6.04)	146	38.09 (5.63)	-0.13 (4.6)	Adj MD (95% CI)=-0.14 (-1.12, 0.84), 0.78
	Dem	QOL-AD (13-52)‡	IG1	6	38.01 (5.44)	134	37.86 (5.13)	-0.70 (4.07)	37.96 (6.04)	139	37.71 (5.91)	-0.43 (5.13)	Adj MD (95% CI)=-0.02 (-1.04, 1.00), 0.97
Pantoni, 2017*[287] Fair	MCI	EQ-5D index value (-1, 1)	IG1	6	0.7 (0.3)	21	NR	0.1 (0.2)	0.7 (0.3)	22	NR	0.1 (0.2)	NR, 0.698
	MCI	EQ-5D index value (-1, 1)	IG1	12	0.7 (0.3)	21	NR	0 (0.3)	0.7 (0.3)	22	NR	0.1 (0.3)	NR, 0.647
	MCI	EQ-VAS (0-100)	IG1	6	63.1 (18.3)	21	NR	5.2 (15.3)	67.3 (17.5)	22	NR	-2.3 (9.2)	NR, 0.057
	MCI	EQ-VAS (0-100)	IG1	12	63.1 (18.3)	21	NR	5.0 (14.2)	67.3 (17.5)	22	NR	-4.3 (16.6)	NR, 0.056
	MCI	SF-36 MCS (0-100)	IG1	6	NR	21	NR	1.4 (5.3)	NR	22	NR	3.0 (11.4)	NR, 0.567
	MCI	SF-36 MCS (0-100)	IG1	12	NR	21	NR	1.3 (7.0)	NR	22	NR	0.2 (9.6)	NR, 0.668
	MCI	SF-36 PCS (0-100)	IG1	6	NR	21	NR	-1.1 (6.5)	NR	22	NR	-1.9 (8.2)	NR, 0.709
	MCI	SF-36 PCS (0-100)	IG1	12	NR	21	NR	-2.0 (8.1)	NR	22	NR	-1.5 (10.2)	NR, 0.867
Vidovich, 2015*[276] Good	MCI	QOL-AD (13-52)	IG1	12	NR	77	NR	0.0 (-0.7, 0.8)	NR	77	NR	-0.9 (-1.6, -0.1)	NR
	MCI	QOL-AD (13-52)	IG1	24	NR	67	NR	-0.1 (-0.9, 0.7)	NR	60	NR	-1.0 (-1.8, -0.2)	NR, 0.018

Appendix G Table 3. Patient-Level Nonpharmacologic Interventions: Detailed Results for Quality of Life Outcomes, by Intervention Type

Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Exercise Interventions													
Hoffmann, 2016*[302] Good	Dem	EQ-5D index value (-0.624-1)‡	IG1	4	0.88 (0.12)	102	0.87 (0.12)	NR	0.86 (0.11)	88	0.85 (0.13)	NR	MDC (95% CI)=0.02 (-0.02, 0.06), 0.300
	Dem	EQ-5D index value (-0.624-1)	IG1	4	0.93 (0.10)	102	0.92 (0.11)	NR	0.93 (0.09)	88	0.92 (0.09)	NR	MDC (95% CI)=0.01 (-0.02, 0.04), 0.402
	Dem	EQ-VAS (0-100)‡	IG1	4	72.9 (18.0)	102	71.1 (19.0)	NR	73.8 (17.1)	88	70.2 (17.2)	NR	MDC (95% CI)=2.0 (-2.7, 6.7), 0.406
	Dem	EQ-VAS (0-100)	IG1	4	83.2 (13.7)	102	82.5 (15.5)	NR	83.3 (15.5)	88	80.7 (16.6)	NR	MDC (95% CI)=2.7 (-2.2, 7.7), 0.283
Lamb, 2018*[306] Good	Dem	EQ-5D-3L (0-1)	IG1	6	0.82 (0.20)	292	0.80 (0.21)	NR	0.85 (0.18)	139	0.83 (0.21)	NR	Adj MD (95% CI)=0.02 (-0.01, 0.06), 0.240
	Dem	EQ-5D-3L (0-1)	IG1	12	0.82 (0.20)	261	0.81 (0.22)	NR	0.85 (0.18)	131	0.82 (0.25)	NR	Adj MD (95% CI)=-0.002 (-0.04, 0.04), 0.928
	Dem	EQ-5D-3L (0-1)‡	IG1	6	0.68 (0.24)	277	0.64 (0.27)	NR	0.70 (0.24)	134	0.65 (0.29)	NR	Adj MD (95% CI)=-0.01 (-0.06, 0.03), 0.53
	Dem	EQ-5D-3L (0-1)‡	IG1	12	0.68 (0.24)	259	0.60 (0.28)	NR	0.70 (0.24)	128	0.60 (0.32)	NR	Adj MD (95% CI)=-0.02 (-0.07, 0.03), 0.43
	Dem	EQ-VAS (0-100)	IG1	6	NR	288	75.4 (20.6)	NR	NR	138	78.7 (18.8)	NR	Adj MD (95% CI)=-0.1 (-3.62, 3.36), 0.942
	Dem	EQ-VAS (0-100)	IG1	12	NR	261	75.5 (19.3)	NR	NR	124	78.3 (19.4)	NR	Adj MD (95% CI)=1.4 (-2.58, 5.23), 0.464

Appendix G Table 3. Patient-Level Nonpharmacologic Interventions: Detailed Results for Quality of Life Outcomes, by Intervention Type

Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Dem	EQ-VAS (0-100)‡	IG1	6	NR	278	66.1 (20.1)	NR	NR	135	65.4 (20.5)	NR	Adj MD (95% CI)=-0.6 (-4.3, 3.1), 0.74
	Dem	EQ-VAS (0-100)‡	IG1	12	NR	260	65.0 (20.0)	NR	NR	128	65.6 (19.9)	NR	Adj MD (95% CI)=1.2 (-2.4, 4.8), 0.52
	Dem	QOL-AD (13-52)	IG1	6	38.7 (5.6)	263	38.9 (6.1)	NR	39.3 (5.2)	124	39.0 (5.9)	NR	Adj MD (95% CI)=-0.1 (-0.98, 0.84), 0.879
	Dem	QOL-AD (13-52)	IG1	12	38.7 (5.6)	237	38.4 (5.8)	NR	39.3 (5.2)	119	39.1 (5.7)	NR	Adj MD (95% CI)=0.7 (-0.21, 1.65), 0.127
	Dem	QOL-AD (13-52)‡	IG1	6	NR	239	31.6 (6.2)	NR	NR	114	31.3 (6.2)	NR	Adj MD (95% CI)=0.1 (-0.9, 1.0), 0.89
	Dem	QOL-AD (13-52)‡	IG1	12	NR	234	30.6 (6.1)	NR	NR	118	30.6 (6.0)	NR	Adj MD (95% CI)=0.02 (-1.0, 1.0), 0.96
Lautenschlager, 2008[292] Good	MCI	SF-36 MCS (0-100)	IG1	6	NR	85	NR	5.13 (3.40, 6.86)	NR	85	NR	4.37 (2.73, 6.01)	NR
	MCI	SF-36 MCS (0-100)	IG1	12	NR	85	NR	6.31 (4.80, 7.82)	NR	85	NR	3.38 (1.63, 5.14)	NR
	MCI	SF-36 MCS (0-100)	IG1	17	NR	85	NR	4.58 (2.38, 6.78)	NR	85	NR	2.74 (0.77, 4.72)	NR, 0.67
	MCI	SF-36 PCS (0-100)	IG1	6	NR	85	NR	-4.04 (-5.71, -2.37)	NR	85	NR	-4.40 (-6.10, -2.70)	NR
	MCI	SF-36 PCS (0-100)	IG1	12	NR	85	NR	-4.49 (-6.03, -2.96)	NR	85	NR	-3.73 (-5.67, -1.79)	NR
	MCI	SF-36 PCS (0-100)	IG1	17	NR	85	NR	-4.85 (-6.78, -2.92)	NR	85	NR	-4.69 (-6.52, -2.87)	NR, 0.95
Multicomponent and Other Interventions													
Jha, 2013*[316] Fair	MCI + Dem	EQ-5D (0-100)	IG1	6	NR	17	64 (12)	3.82 (NR)	NR	17	66 (10)	-2.1 (NR)	NR, 0.66
	MCI + Dem	WHO-5 (0-100)	IG1	6	NR	17	61 (10)	18.3 (NR)	NR	17	58 (13)	9.46 (NR)	NR, 0.03
Marshall, 2015*[315] Fair	Dem	QOL-AD (13-52)‡	IG1	3	31.5 (6.6)	28	30.3 (7.0)	NR	33.6 (5.7)	27	32.5 (6.6)	NR	MDC (95% CI)=-0.50 (-2.90, 1.88), NS

Appendix G Table 3. Patient-Level Nonpharmacologic Interventions: Detailed Results for Quality of Life Outcomes, by Intervention Type

Author, year Quality	Pop cat	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Dem	QOL-AD (13-52)‡	IG1	5	31.5 (6.6)	28	30.8 (6.7)	NR	33.6 (5.7)	24	32.9 (5.2)	NR	MDC (95% CI)=-0.31 (-3.09, 2.47), NS
	Dem	QOL-AD (13-52)	IG1	3	34.4 (5.8)	28	35.4 (7.2)	NR	37.5 (4.6)	27	36.3 (6.5)	NR	MDC (95% CI)=2.12 (-0.17, 4.42), NS
	Dem	QOL-AD (13-52)	IG1	5	34.4 (5.8)	28	35.9 (6.3)	NR	37.5 (4.6)	24	38.7 (5.8)	NR	MDC (95% CI)=0.30 (-2.09, 2.69), NS
Quinn, 2016*[314] Good	Dem	EQ-5D-3L (0-1)	IG1	3	NR	13	NR	NR	NR	11	NR	NR	Adj MD (95% CI)=0.05 (-0.05, 0.14), NS
	Dem	EQ-5D-3L (0-1)	IG1	6	NR	13	NR	NR	NR	11	NR	NR	Adj MD (95% CI)=-0.04 (-0.15, 0.07), NS
Wolfs, 2008[313] Fair	MCI + Dem	EQ-5D index value (0-1)‡	IG1	6	0.54 (0.33)	116	0.58 (0.33)	NR	0.54 (0.30)	83	0.53 (0.33)	NR	MDC (95% CI)=0.1 (-0.04, 0.12), NS
	MCI + Dem	EQ-5D index value (0-1)‡	IG1	12	0.54 (0.33)	113	0.49 (0.35)	NR	0.54 (0.30)	77	0.43 (0.34)	NR	MDC (95% CI)=0.1 (-0.04, 0.14), NS
	MCI + Dem	EQ-VAS (0-100)‡	IG1	6	58.7 (20.7)	116	60.2 (18.3)	NR	60.0 (19.3)	83	56.1 (18.8)	NR	MDC (95% CI)=5.4 (0.29, 10.45), 0.04
	MCI + Dem	EQ-VAS (0-100)‡	IG1	12	58.7 (20.7)	113	58.3 (20.5)	NR	60.0 (19.3)	77	54.4 (21.8)	NR	MDC (95% CI)=5.2 (-0.58, 10.94), NS

* New study
† Higher values indicate better outcomes for all instruments
‡ Caregiver-reported
§ Combined patient- and caregiver-reported
‖ Standard error

Abbreviations: Adj MD = adjusted mean difference; BL = baseline; CG = control group; CI = confidence interval; Dem = dementia; DEMQOL = Dementia Quality of Life; EQ-5D-3L = EuroQol 5-Dimensions 3 Level; EQ-5D Index = EuroQol 5-Dimensions; EQ-VAS = EuroQol Visual Analog Scale; ES = effect size; FU = followup; IG = intervention

Appendix G Table 3. Patient-Level Nonpharmacologic Interventions: Detailed Results for Quality of Life Outcomes, by Intervention Type

group; Int arm = intervention arm; MCI = mild cognitive impairment; MDC = mean difference in change; mo. = months; Pop cat = population category; QOL-AD = Quality of Life in Alzheimer's Disease; NR = not reported; NS = Not statistically significant; SD = standard deviation; SF-36 MCS = Short Form 36-item, Mental Component Summary; SF-36 PCS = Short Form 36-item, Physical Component Summary; WHO-5 = World Health Organization Well-Being Index

Appendix G Table 4. Patient-Level Nonpharmacologic Interventions: Detailed Results for Mental Health and Neuropsychiatric Symptom Outcomes, by Intervention Type

Author, year Quality	Pop cat	Symptom (Instrument, range†)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Cognitive Stimulation, Training, and Rehabilitation													
Amieva, 2016*[275] Good	Dem	Dep (MADRS, 0-60)	IG1	3	NR	151	10.65 (9.9)	NR	NR	141	8.82 (9.1)	NR	NR, 0.0590
	Dem	Dep (MADRS, 0-60)	IG1	24	NR	124	20.21 (17.2)	NR	NR	109	18.51 (17.1)	NR	NR, 0.3127
	Dem	Dep (MADRS, 0-60)	IG2	3	NR	144	10.00 (9.9)	NR	NR	141	8.82 (9.1)	NR	NR, 0.3221
	Dem	Dep (MADRS, 0-60)	IG2	24	NR	121	16.82 (16.4)	NR	NR	109	18.51 (17.1)	NR	NR, 0.4953
	Dem	NPS (NPI-12, 0-144)	IG1	3	NR	151	25.34 (28.8)	NR	NR	141	23.29 (28.4)	NR	NR, 0.2224
	Dem	NPS (NPI-12, 0-144)	IG1	24	NR	124	41.52 (32.1)	NR	NR	109	39.31 (32.3)	NR	NR, 0.5313
	Dem	NPS (NPI-12, 0-144)	IG2	3	NR	144	24.64 (29.2)	NR	NR	141	23.29 (28.4)	NR	NR, 0.6847
	Dem	NPS (NPI-12, 0-144)	IG2	24	NR	121	34.44 (32.8)	NR	NR	109	39.31 (32.3)	NR	NR, 0.0808
Belleville, 2018*[289] Fair	MCI	Anx (GAI, 0-20)	IG1	3	4.92 (5.04)	36	5.42 (5.06)	NR	5.38 (5.06)	38	4.32 (4.83)	NR	NS
	MCI	Anx (GAI, 0-20)	IG1	6	4.92 (5.04)	36	4.56 (5.14)	NR	5.38 (5.06)	38	4.73 (5.18)	NR	NS
	MCI	Dep (GDS-15, 0-15)	IG1	3	3.00 (3.11)	36	3.39 (3.47)	NR	3.23 (2.82)	38	3.47 (2.45)	NR	NS
	MCI	Dep (GDS-15, 0-15)	IG1	6	3.00 (3.11)	36	2.67 (3.29)	NR	3.23 (2.82)	38	3.27 (2.24)	NR	NS
Bergamaschi, 2013*[280] Fair	Dem	Dep (CSDD, 0-38)	IG1	12	NR	16	30.44 (4.87)	NR	NR	16	26.75 (7.73)	NR	NS
Buschert, 2011[269]	MCI	Dep (MADRS, 0-60)	IG1	6	3.6 (2.6)	10	0.7 (1.3)	NR	3.7 (5.9)	12	3.8 (6.1)	NR	NR, <0.01
Fair	Dem	Dep (MADRS, 0-60)	IG1	6	3.1 (4.1)	8	1.6 (3.4)	NR	4.3 (4.0)	7	4.7 (4.0)	NR	NR, 0.09
Cavallo, 2016*[284] Good	Dem	Dep (HADS-D, 0-21)	IG1	3	6.87 (2.41)	38	6.42 (2.21)	NR	6.05 (2.31)	38	6.35 (2.21)	NR	NS
	Dem	Dep (HADS-D, 0-21)	IG1	6	6.87 (2.41)	38	NR	NR	6.05 (2.31)	38	NR	NR	NS
	Dem	Anx (HADS-A, 0-21)	IG1	3	8.60 (2.77)	38	7.65 (2.41)	NR	7.97 (1.29)	38	7.57 (1.33)	NR	NS
Cavallo, 2016*[284] Good	Dem	Anx (HADS-A, 0-21)	IG1	6	8.60 (2.77)	38	NR	NR	7.97 (1.29)	38	NR	NR	NS
Chapman, 2004[266]	Dem	NPS (NPI-12, 0-144)	IG1	4	NR	26	11.4 (NR)	NR	NR	28	12.4 (NR)	NR	NR
Fair	Dem	NPS (NPI-12, 0-144)	IG1	7	NR	26	10.4 (NR)	NR	NR	28	13.4 (NR)	NR	NR

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Author, year Quality	Pop cat	Symptom (Instrument, range†)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Dem	NPS (NPI-12, 0-144)	IG1	12	NR	26	10.2 (NR)	-2.25 (-7.76, 3.26)	NR	28	17.7 (NR)	2.19 (-3.49, 7.87)	ES=0.36, NS
Greenaway, 2012[271] Fair	MCI	Dep (CES-D, 0-60)	IG1	6	NR	18	8.7 (10.0)	-0.3 (5.8)	NR	17	8.1 (6.1)	-0.5 (3.7)	Cohen's d=0.03, NS
Jeong, 2016*[274] Fair	MCI	Dep (GDS-15, 0-15)	IG1	3	NR	71	NR	-0.4 (2.7)	NR	76	NR	-0.2 (2.9)	NR, 0.11
	MCI	Dep (GDS-15, 0-15)	IG1	9	NR	67	NR	-0.1 (2.6)	NR	62	NR	-0.5 (3.3)	NR, 0.24
	MCI	Dep (GDS-15, 0-15)	IG2	3	NR	77	NR	-0.8 (2.5)	NR	76	NR	-0.2 (2.9)	NR, 0.20
	MCI	Dep (GDS-15, 0-15)	IG2	9	NR	68	NR	-0.7 (2.5)	NR	62	NR	-0.5 (3.3)	NR, 0.33
	MCI	NPS (NPI-12, 0-144)	IG1	3	4.7 (8.4)	71	NR	-1.8 (7.1)	4.1 (5.3)	76	NR	1.3 (9.1)	NR, 0.07
	MCI	NPS (NPI-12, 0-144)	IG1	9	4.7 (8.4)	67	NR	-1.6 (8.8)	4.1 (5.3)	62	NR	1.5 (8.9)	NR, 0.03
	MCI	NPS (NPI-12, 0-144)	IG2	3	3.4 (4.9)	77	NR	0.9 (5.6)	4.1 (5.3)	76	NR	1.3 (9.1)	NR, 0.45
	MCI	NPS (NPI-12, 0-144)	IG2	9	3.4 (4.9)	68	NR	-0.6 (5.0)	4.1 (5.3)	62	NR	1.5 (8.9)	NR, 0.16
Kurz, 2012[272] Fair	Dem	Dep (GDS-15, 0-15)	IG1	3	8.54 (4.83)	92	NR	-1.58 (3.83)	9.25 (5.47)	97	NR	-0.75 (4.13)	NR, 0.16
	Dem	Dep (GDS-15, 0-15)	IG1	9	8.54 (4.83)	83	NR	-1.23 (4.48)	9.25 (5.47)	88	NR	-0.41 (3.86)	NR, 0.20
	Dem	NPS (NPI-12, 0-12)	IG1	3	6.77 (6.798)	92	NR	0.11 (6.429)	7.94 (7.802)	97	NR	-1.38 (6.087)	NR, 0.103
	Dem	NPS (NPI-12, 0-12)	IG1	9	6.77 (6.798)	83	NR	1.16 (8.658)	7.94 (7.802)	88	NR	0.42 (6.874)	NR, 0.539
Olazaran, 2004[265] Fair	MCI + Dem	Dep (GDS-15, 0-15)	IG1	3	3.0 (0.3)‡	40	NR	0 (NR)	3.4 (0.4)‡	40	NR	-0.5 (NR)	NS
	MCI + Dem	Dep (GDS-15, 0-15)	IG1	6	3.0 (0.3)‡	40	NR	0 (NR)	3.4 (0.4)‡	40	NR	-0.5 (NR)	NS
	MCI + Dem	Dep (GDS-15, 0-15)	IG1	12	3.0 (0.3)‡	40	NR	-0.5 (NR)	3.4 (0.4)‡	40	NR	0.25 (NR)	NR, 0.05
Orrell, 2014*[279] Good	Dem	NPS (NPI-10, 0-120)	IG1	3	NR	123	14.71 (2.84)‡	NR	NR	113	16.18 (2.76)‡	NR	Adj MD=1.47 (-1.59, 4.53), 0.34
	Dem	NPS (NPI-10, 0-120)	IG1	6	NR	123	18.76 (3.78)‡	NR	NR	113	20.35 (3.94)‡	NR	Adj MD=1.58 (-2.67, 5.84), 0.53
Orrell, 2017*[273] Good	Dem	Dep (GDS-15, 0-15)	IG1	3	NR	142	2.98 (2.56)	-0.14 (1.98)	NR	146	3.03 (2.86)	0.11 (2.24)	Adj MD=-0.09 (-0.56, 0.38), 0.71
	Dem	Dep (GDS-15, 0-15)	IG1	6	NR	134	2.90 (2.55)	-0.11 (1.94)	NR	139	2.85 (2.67)	-0.09 (2.7)	Adj MD=--0.02(-0.51, 0.47), 0.94

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	Dem	NPS (NPI-12, 0-144)	IG1	3	11.21 (13.96)	142	10.67 (13.30)	0.21 (11.05)	10.99 (11.98)	146	12.07 (12.61)	1.96 (10.08)	Adj MD=--1.45 (-3.68, 0.76), 0.20
	Dem	NPS (NPI-12, 0-144)	IG1	6	11.21 (13.96)	134	11.57 (13.72)	1.14 (11.72)	10.99 (11.98)	139	11.59 (12.80)	1.40 (10.1)	Adj MD=--0.32 (-2.78, 2.12), 0.79
Pantoni, 2017*[287] Fair	MCI	Dep (GDS-15, 0-15)	IG1	6	4.6 (4.0)	21	NR	-0.1 (2.1)	4.9 (3.8)	22	NR	-0.8 (2.9)	NR, 0.393
	MCI	Dep (GDS-15, 0-15)	IG1	12	4.6 (4.0)	21	NR	-0.1 (2.9)	4.9 (3.8)	22	NR	-0.7 (2.5)	NR, 0.448
Vidovich, 2015*[276] Good	MCI	Dep (PHQ-9, 0-27)	IG1	12	NR	77	NR	0.1 (-0.9, 1.1)	NR	77	NR	-0.4 (-1.3, 0.4)	NR
	MCI	Dep (PHQ-9, 0-27)	IG1	24	NR	67	NR	-0.4 (-1.2, 0.5)	NR	60	NR	-0.2 (-1.0, 0.6)	NR, 0.953
Exercise Interventions													
Ho, 2018*[308] Fair	MCI + Dem	Dep (GDS-4, 0-4)	IG1	3	0.8 (1.1)	69	0.6 (0.9)	NR	0.9 (1.1)	68	1.2 (1.2)	NR	Beta (SE)=-0.51 (0.19), <0.01
	MCI + Dem	Dep (GDS-4, 0-4)	IG1	6	0.8 (1.1)	69	0.7 (1.0)	NR	0.9 (1.1)	68	1.1 (1.1)	NR	NS
	MCI + Dem	Dep (GDS-4, 0-4)	IG1	12	0.8 (1.1)	69	0.7 (1.0)	NR	0.9 (1.1)	68	1.0 (1.0)	NR	NS
	MCI + Dem	Dep (GDS-4, 0-4)	IG2	3	1.1 (1.2)	67	1.0 (1.2)	NR	0.9 (1.1)	68	1.2 (1.2)	NR	Beta (SE)=-0.30 (0.20), 0.13
	MCI + Dem	Dep (GDS-4, 0-4)	IG2	6	1.1 (1.2)	67	1.3 (1.3)	NR	0.9 (1.1)	68	1.1 (1.1)	NR	NS
	MCI + Dem	Dep (GDS-4, 0-4)	IG2	12	1.1 (1.2)	67	1.2 (1.4)	NR	0.9 (1.1)	68	1.0 (1.0)	NR	NS
	MCI + Dem	NPS (NPI-Q-12, 0-36)	IG1	3	3.1 (3.7)	69	2.5 (4.4)	NR	2.8 (4.6)	68	2.2 (3.0)	NR	Beta (SE)=0.01 (0.65), 0.98
	MCI + Dem	NPS (NPI-Q-12, 0-36)	IG1	6	3.1 (3.7)	69	2.7 (3.9)	NR	2.8 (4.6)	68	1.5 (2.5)	NR	NS
	MCI + Dem	NPS (NPI-Q-12, 0-36)	IG1	12	3.1 (3.7)	69	2.8 (4.5)	NR	2.8 (4.6)	68	1.7 (2.7)	NR	NS
	MCI + Dem	NPS (NPI-Q-12, 0-36)	IG2	3	2.6 (4.1)	67	2.8 (4.7)	NR	2.8 (4.6)	68	2.2 (3.0)	NR	Beta (SE)=1.04 (0.63), 0.10
	MCI + Dem	NPS (NPI-Q-12, 0-36)	IG2	6	2.6 (4.1)	67	2.8 (3.7)	NR	2.8 (4.6)	68	1.5 (2.5)	NR	NS

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	MCI + Dem	NPS (NPI-Q-12, 0-36)	IG2	12	2.6 (4.1)	67	2.5 (4.5)	NR	2.8 (4.6)	68	1.7 (2.7)	NR	NS
Hoffmann, 2016*[302] Good	Dem	Dep (HDRS, 0-52)	IG1	4	1.9 (2.6)	102	1.7 (2.5)	NR	2.0 (2.5)	88	1.8 (2.3)	NR	MDC=-0.1 (-0.7, 0.5), 0.791
	Dem	NPS (NPI-12, 0-144)	IG1	4	10.0 (10.8)	102	8.8 (8.5)	NR	9.4 (9.7)	88	11.4 (11.0)	NR	MDC=-3.5 (-5.8, -1.3), 0.002
Holthoff, 2015*[303] Fair	Dem	NPS (NPI-12, 0-144)	IG1	3	NR	15	10.05 (1.26)‡	NR	NR	15	15.71 (1.26)‡	NR	Adj MD (95% CI)=5.66 (-9.28, -2.03), NR
	Dem	NPS (NPI-12, 0-144)	IG1	6	NR	13	10.40 (1.38)‡	NR	NR	14	16.09 (1.29)‡	NR	Adj MD (95% CI)=5.69 (-9.55, -1.83), <0.05
Lam, 2011[293] Fair	MCI	Dep (CSDD, 0-38)	IG1	5	0.9 (1.8)	135	0.7 (0.9)	NR	0.8 (1.8)	194	0.6 (0.9)	NR	NS
	MCI	NPS (NPI-12, 0-12)	IG1	5	0.6 (0.9)	135	0.5 (0.9)	NR	0.6 (0.9)	194	0.7 (1.0)	NR	NS
Lamb, 2018*[306] Good	Dem	NPS (NPI-12, 0-144)	IG1	6	12.8 (15.0)	234	15.2 (16.1)	NR	13.3 (13.2)	110	14.8 (15.6)	NR	Adj MD (95% CI)=-0.5 (-3.08, 2.05), 0.695
	Dem	NPS (NPI-12, 0-144)	IG1	12	12.8 (15.0)	215	16.2 (15.9)	NR	13.3 (13.2)	105	13.5 (13.1)	NR	Adj MD (95% CI)=-2.1 (-4.83, 0.65), 0.135
Lautenschlager, 2008[292] Good	MCI	Dep (BDI, 0-63)	IG1	6	NR	85	NR	-0.94 (-1.77, -0.12)	NR	85	NR	-0.75 (-1.62, 0.13)	NR
	MCI	Dep (BDI, 0-63)	IG1	12	NR	85	NR	-0.75 (-1.62, 0.12)	NR	85	NR	-0.44 (-1.29, 0.40)	NR
	MCI	Dep (BDI, 0-63)	IG1	17	NR	85	NR	-0.46 (-1.47, 0.55)	NR	85	NR	-0.51 (-1.44, 0.42)	NR, 0.44
Lazarou, 2017*[299] Fair	MCI	NPS (NPI-12, 0-144)	IG1	10	3.18 (4.91)	66	1.78 (2.28)	NR	2.97 (4.04)	63	3.76 (4.84)	NR	NR, 0.02
Marshall, 2015*[315] Fair	Dem	Dep (CSDD, 0-38)	IG1	3	11 (39.3)§	28	12 (42.8)§	NR	7 (25.9)§	27	6 (22.2)§	NR	NR
	Dem	Dep (CSDD, 0-38)	IG1	5	11 (39.3)§	28	7 (25.0)§	NR	7 (25.9)§	24	6 (25.0)§	NR	NR
Morris, 2017*[301] Good	MCI + Dem	Dep (CSDD, 0-38)	IG1	3	8.6 (5.1)	36	8.4 (4.6)	NR	7.4 (3.8)	37	8.1 (4.4)	NR	NR

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	MCI + Dem	Dep (CSDD, 0-38)	IG1	6	8.6 (5.1)	34	7.8 (5.2)	NR	7.4 (3.8)	34	7.8 (4.4)	NR	ES=0.98 (-2.65, 0.69), 0.51
Pitkälä, 2013*[290] Good	Dem	Dep (CSDD, 0-38)	IG1	12	NR	57	NR	1.35 (0.14, 2.66)	NR	59	NR	0.04 (-1.56, 1.40)	NR, 0.81
	Dem	Dep (CSDD, 0-38)	IG2	12	NR	63	NR	0.5 (-0.67, 1.54)	NR	59	NR	0.04 (-1.56, 1.40)	NR, 0.81
	Dem	NPS (NPI-12, 0-144)	IG2	6	NR	63	NR	2.73 (1.08, 5.05)	NR	59	NR	0.64 (-2.23, 3.46)	NR, 0.41
	Dem	NPS (NPI-12, 0-144)	IG1	6	NR	61	NR	0.88 (-1.30, 2.84)	NR	65	NR	0.64 (-2.23, 3.46)	NR, 0.41
Vreugdenhil, 2012[298] Fair	Dem	Dep (GDS-15, 0-15)	IG1	4	2.6 (1.7)	20	2.0 (1.5)	-0.5 (0.2)‡	2.3 (1.4)	20	2.3 (1.4)	0.2 (0.3)‡	NR, 0.071
Multicomponent and Other Interventions													
Bae, 2019*[320] Fair	MCI	Dep (GDS-15, 0-15)	IG1	6	2.9 (2.2)	41	NR	-0.11 (-0.84, 0.61)	2.9 (2.7)	42	NR	0.36 (-0.32, 1.04)	NR, 0.35
Belleville, 2018*[289] Fair	MCI	Anx (GAI, 0-20)	IG1	3	5.42 (4.75)	40	5.75 (4.74)	NR	5.38 (5.06)	38	4.32 (4.83)	NR	NS
	MCI	Anx (GAI, 0-20)	IG1	6	5.42 (4.75)	31	5.52 (5.55)	NR	5.38 (5.06)	38	4.73 (5.18)	NR	NS
	MCI	Dep (GDS-15, 0-15)	IG1	3	3.56 (3.17)	40	3.38 (3.19)	NR	3.23 (2.82)	38	3.47 (2.45)	NR	NS
	MCI	Dep (GDS-15, 0-15)	IG1	6	3.56 (3.17)	31	3.36 (2.92)	NR	3.23 (2.82)	38	3.27 (2.24)	NR	NS
Burgener, 2008[312] Fair	Dem	Dep (GDS-15, 0-15)	IG1	5	NR	19	3.3 (2.9)	0.4 (NR)	NR	14	4.3 (3.4)	0.9 (NR)	NR, 0.37
Jha, 2013*[316] Fair	MCI + Dem	Dep (CSDD, 0-38)	IG1	6	NR	16	4.0 (1.7)	-2.56 (NR)	NR	17	4.5 (1.8)	-2.53 (NR)	NR, 0.38
Marshall, 2015*[315] Fair	Dem	Dep (CSDD, 0-38)	IG1	3	NR	28	6.7 (4.2)	NR	NR	27	5.0 (4.5)	NR	MDC=0.11 (-2.02, 2.25),
	Dem	Dep (CSDD, 0-38)	IG1	5	NR	28	7.0 (4.6)	NR	NR	24	5.4 (4.0)	NR	MDC=0.29 (-2.08, 2.67),
Quinn, 2016*[314] Good	Dem	Dep (HDRS, 0-21)	IG1	6	NR	13	NR	NR	NR	11	NR	NR	Adj MD:0.96 (-1.58, 3.49), NS
	Dem	Anx (HADS-A, 0-21)	IG1	3	NR	13	NR	NR	NR	11	NR	NR	Adj MD (95% CI)=0.8 (-3.07, 1.47), NS

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Quinn, 2016*[314] Good	Dem	Anx (HADS-A, 0-21)	IG1	6	NR	13	NR	NR	NR	11	NR	NR	Adj MD (95% CI)=1.14 (-3.41, 1.13), NS
Richard, 2009[317] Fair	Dem	NPS (RMBPC, Total freq, 0-100)	IG1	12	25.5 (10.3)	57	30.3 (13.6)	NR	26.1 (9.9)	48	31.9 (12.5)	NR	NS
	Dem	NPS (RMBPC, Total freq, 0-100)	IG1	24	25.5 (10.3)	50	31.1 (14.7)	11.17 (13.1)	26.1 (9.9)	44	37.3 (15.4)	6.63 (12.8)	MDC=4.54 (-1.39, 10.49), 0.35
Rovner, 2018*[318] Good	MCI	Dep (GDS-15, 0-15)	IG1	24	3.7 (3.1)	111	NR	-0.07 (-0.33, 0.18)	3.2 (3.0)	110	NR	-0.14 (-0.38, 0.10)	Beta (95% CI)=0.07 (-0.28, 0.41), 0.709
Straubmeier, 2017*[322] Fair	MCI + Dem	NPS (NPI-Q-12, 0-36)	IG1	6	5.2 (2.7)	208	NR	0.16 (1.8)	5.3 (2.7)	154	NR	-0.27 (1.9)	ES=0.23, 0.055
Wolfs, 2008[313] Fair	MCI + Dem	Dep (CSDD, 0-38)	IG1	6	7.9 (4.3)	116	7.2 (4.7)	NR	7.4 (3.8)	83	7.9 (5.0)	NR	MDC=-1.3 (-2.62, 0.07), NS
	MCI + Dem	Dep (CSDD, 0-38)	IG1	12	7.9 (4.3)	113	7.5 (5.0)	NR	7.4 (3.8)	77	7.8 (4.9)	NR	MDC=-0.8 (-2.24, 0.69), NS
	MCI + Dem	NPS (NPI-12, 0-144)	IG1	6	23.4 (15.6)	116	24.3 (18.5)	NR	22.6 (16.5)	83	27.3 (20.8)	NR	MDC=-4.0 (-8.46, 0.54), NS
	MCI + Dem	NPS (NPI-12, 0-144)	IG1	12	23.4 (15.6)	113	28.4 (20.8)	NR	22.6 (16.5)	77	29.0 (21.0)	NR	MDC=-1.2 (-6.06, 3.63), NS

* New study

† Lower values indicate better outcomes for all instruments

‡ Standard error

§ N (%) participants with CSDD score ≥7 (indicator for clinically significant levels of depression)

Abbreviations: Anx = Anxiety; BDI = Beck Dep Inventory; BL = baseline; CG = control group; CI = confidence interval; CSDD = Cornell Scale for Depression in Dementia; Dem = dementia; freq. = frequency; Dep = depression; FU = followup; GDS-15 = Geriatric Depression Scale-15 item; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; HADS-A = Hospital Anxiety and Depression Scale – Depression subscale; HDRS = Hamilton Depression Rating Scale; IG = intervention group; Int arm = intervention arm; MADRS = Montgomery-Åsberg Depression Rating Scale; MCI = mild cognitive impairment; MDC = mean difference in change; mo. = months; NPI-10 = Neuropsychiatric Inventory-10 item; NPI-12 = Neuropsychiatric Inventory-12 item; NPS = Composite neuropsychiatric symptoms; NR = not reported; PHQ-9 = Patient Health Quesionnaire-9 item; Pop cat = population category; RMBPC = Revised Memory and Behavior Problems Checklist; SD = standard deviation

Appendix H Table 1. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Burden Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Psychoeducation Interventions													
Berwig, 2017*[327] Fair	Caregiver	RMBPC Disruptive behaviors (total burden) (0-96)	IG1	6	21.1 (9.1)	41	NR	-5.461 (7.257)	16.6 (9.6)	40	NR	2.342 (6.379)	ES=1.144, 0.000
	Caregiver	RMBPC Disruptive behaviors (total burden) (0-96)	IG1	9	21.1 (9.1)	31	NR	-6.173 (7.865)	16.6 (9.6)	31	NR	3.243 (6.999)	ES=1.267, 0.000
	Caregiver	Zarit-22 (0-88)	IG1	6	32.5 (12.8)	41	NR	-0.425 (8.409)	28.16 (12.5)	40	NR	7.047 (8.093)	ES=0.906, 0.000
	Caregiver	Zarit-22 (0-88)	IG1	9	32.5 (12.8)	31	NR	2.669 (8.858)	28.16 (12.5)	31	NR	8.102 (8.576)	ES=0.623, 0.017
Brennan, 1995[328] Fair	Caregiver	Impact of Caregiving Scale (Emotional Impact) (NR)	IG1	12	11.4 (3.2)	47	11.0 (3.4)	NR	11.6 (2.0)	49	10.9 (2.5)	NR	NR, 0.65
	Caregiver	Impact of Caregiving Scale (Physical Impact) (NR)	IG1	12	10.8 (3.3)	47	11.4 (4.0)	NR	10.5 (3.5)	49	11.6 (3.9)	NR	NR, 0.47
	Caregiver	Impact of Caregiving Scale (Relational Impact) (NR)	IG1	12	12.2 (3.5)	47	12.1 (3.9)	NR	12.0 (3.4)	49	11.5 (3.3)	NR	NR, 0.63
	Caregiver	Impact of Caregiving Scale (Social Impact) (NR)	IG1	12	13.7 (2.1)	47	12.8 (3.2)	NR	14.0 (2.3)	49	12.9 (2.7)	NR	NR, 0.56
Burgio, 2003[330] Fair	Caregiver	RMBPC (average burden) (0-4)	IG1 (Black)	6	1.35 (1.10)	20	0.91 (0.88)	NR	1.73 (1.18)	20	1.77 (1.14)	NR	NR
	Caregiver	RMBPC (average burden) (0-4)	IG1 (White)	6	1.62 (1.06)	27	1.54 (1.02)	NR	1.50 (0.88)	29	1.15 (0.83)	NR	NR
	Caregiver	RMBPC (total burden) (0-96)	IG1	6	19.0 (15.9)	47	13.6 (1.7)	NR	19.9 (15.9)	52	15.0 (1.7)	NR	NR, 0.52
Chu, 2011[332] Fair	Caregiver	CBI (0-96)	IG1	3	79.79 (NR)	30	75.03 (NR)	NR	76.01 (NR)	30	75.00 (NR)	NR	NR, 0.16
	Caregiver	CBI (0-96)	IG1	4	79.79 (NR)	30	77.29 (NR)	NR	76.01 (NR)	30	76.22 (NR)	NR	NR, 0.36

Appendix H Table 1. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Burden Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Cristancho-Lacroix, 2015*[334] Fair	Caregiver	RMBPC (average burden) (0-4)	IG1	3	2.2 (0.4)	25	2.2 (0.6)	0.0 (0.4)	2.2 (0.6)	24	2.1 (0.6)	-0.1 (0.5)	NR, 0.66
	Caregiver	RMBPC (average burden) (0-4)	IG1	6	2.2 (0.4)	25	2.3 (0.5)	NR	2.2 (0.6)	24	2.1 (0.6)	NR	NS
	Caregiver	Zarit-22 (0-88)	IG1	3	38.0 (14.5)	25	38.3 (14.9)	0.3 (6.6)	35.0 (15.0)	24	33.5 (15.3)	-1.5 (6.1)	NR, 0.74
	Caregiver	Zarit-22 (0-88)	IG1	6	38.0 (14.5)	25	39.6 (15.7)	NR	35.0 (15.0)	24	34.8 (15.9)	NR	NS
De Rotrou, 2011[335] Fair	Caregiver	Zarit-22 (0-88)	IG1	3	23.0 (14.2)	62	22.2 (12.5)	NR	24.3 (16.9)	64	23.6 (17.0)	NR	MD=0.55, NR
	Caregiver	Zarit-22 (0-88)	IG1	6	23.0 (14.2)	55	23.0 (14.6)	NR	24.3 (16.9)	56	26.5 (17.0)	NR	MD=0.25, NR
Finkel, 2007[338] Fair	Caregiver	RMBPC (total burden) (0-96)	IG1	6	15.7 (NR)	13	10.4 (NR)	NR	15.7 (NR)	12	16.9 (NR)	NR	Cohen's D: 0.77, 0.089
Fung, 2002*[339] Fair	Caregiver	NPI-12 (0-60)	IG1	4	47.20 (10.11)	26	36.80 (9.38)	NR	47.87 (12.68)	26	42.49 (13.56)	NR	F statistic=5.099, 0.003
Gallagher-Thompson, 2003[340] Fair	Caregiver	RMBPC (average burden) (0-4)	IG1 (Hispanic)	6	18.24 (14.39)	32	13.69 (1.85)	NR	16.02 (9.24)	14	16.35 (2.81)	NR	NR
	Caregiver	RMBPC (average burden) (0-4)	IG1 (White)	6	19.27 (10.68)	41	14.69 (1.29)	NR	19.22 (14.08)	18	15.50 (1.94)	NR	NR
Gallagher-Thompson, 2008[341] Fair	Caregiver	RMBPC (average burden) (0-4)	IG1 (Hispanic)	6	1.30 (1.05)	47	1.24 (0.85)	NR	1.22 (0.93)	42	1.15 (0.84)	NR	NR
	Caregiver	RMBPC (average burden) (0-4)	IG1 (White)	6	1.58 (0.95)	50	1.24 (0.84)	NR	1.61 (0.64)	45	1.57 (0.65)	NR	NR
Gallagher-Thompson, 2010*[342] Good	Caregiver	RMBPC (average burden) (0-4)	IG1	4	1.60 (0.62)	36	1.23 (0.41)	NR	1.56 (0.65)	34	1.54 (0.61)	NR	Beta=-0.286, 0.012
Gaugler, 2013*[344] Fair	Family	RMBPC (total burden) (0-96)	IG1	8	27.25 (14.38)	54	NR	NR	25.07 (14.00)	53	NR	NR	Beta (SE)=-3.26 (2.21), NS
	Family	RMBPC (total burden) (0-96)	IG1	12	27.25 (14.38)	54	NR	NR	25.07 (14.00)	53	NR	NR	Beta (SE)=-2.16 (0.67), <0.01
	Family	RMBPC (total burden) (0-96)	IG1	18	27.25 (14.38)	54	NR	NR	25.07 (14.00)	53	NR	NR	Beta (SE)=-1.82 (1.19), NS
Gaugler, 2013*[344] Fair	Family	RMBPC Depressive behaviors (total burden) (0-36)	IG1	8	11.68 (7.97)	54	NR	NR	10.43 (8.31)	53	NR	NR	Beta (SE)=-0.62 (1.33), NS

Appendix H Table 1. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Burden Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Family	RMBPC Depressive behaviors (total burden) (0-36)	IG1	12	11.68 (7.97)	54	NR	NR	10.43 (8.31)	53	NR	NR	Beta (SE)=-1.58 (0.98), NS
	Family	RMBPC Depressive behaviors (total burden) (0-36)	IG1	18	11.68 (7.97)	54	NR	NR	10.43 (8.31)	53	NR	NR	Beta (SE)=-0.44 (0.66), NS
	Family	RMBPC Disruptive behaviors (total burden) (0-32)	IG1	8	7.90 (6.07)	54	NR	NR	6.08 (5.00)	53	NR	NR	Beta (SE)=-3.23 (1.00), <0.01
	Family	RMBPC Disruptive behaviors (total burden) (0-32)	IG1	12	7.90 (6.07)	54	NR	NR	6.08 (5.00)	53	NR	NR	Beta (SE)=-2.27 (0.71), <0.01
	Family	RMBPC Disruptive behaviors (total burden) (0-32)	IG1	18	7.90 (6.07)	54	NR	NR	6.08 (5.00)	53	NR	NR	Beta (SE)=-1.34 (0.43), <0.01
	Family	RMBPC Memory problems (total burden) (0-28)	IG1	8	8.04 (5.15)	54	NR	NR	8.56 (5.43)	53	NR	NR	Beta (SE)=-0.48 (0.76), NS
	Family	RMBPC Memory problems (total burden) (0-28)	IG1	12	8.04 (5.15)	54	NR	NR	8.56 (5.43)	53	NR	NR	Beta (SE)=-0.48 (0.56), NS
	Family	RMBPC Memory problems (total burden) (0-28)	IG1	18	8.04 (5.15)	54	NR	NR	8.56 (5.43)	53	NR	NR	Beta (SE)=-0.20 (0.42), NS
Gitlin, 2001[345] Fair	Caregiver	MBPC (average) (0-1)	IG1	3	0.48 (0.27)	93	0.43 (0.31)	NR	0.47 (0.30)	78	0.45 (0.29)	NR	Adj MD (95% CI)=-0.02 (-0.09, 0.05), 0.50
Gitlin, 2003[347] Fair	Caregiver	RMBPC (total burden) (0-96)	IG1	6	15.76 (13.84)	89	12.09 (1.00)	NR	13.90 (13.87)	102	14.16 (0.93)	NR	NR, 0.12
Gitlin, 2003[347] Fair	Caregiver	RMBPC Disruptive behaviors (average burden) (0-4)	IG1	6	0.53 (0.53)	89	0.43 (0.50)	NR	0.56 (0.66)	101	0.50 (0.67)	NR	Adj MD (95% CI)=-0.05 (-0.19, 0.09), 0.47
	Caregiver	RMBPC Memory problems (average burden) (0-4)	IG1	6	0.81 (0.86)	89	0.65 (0.75)	NR	0.72 (0.77)	101	0.78 (0.85)	NR	Adj MD (95% CI)=-0.17 (-0.35, -0.02), 0.03

Appendix H Table 1. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Burden Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Gitlin, 2008[346] Fair	Caregiver + patient	RMBPC (average burden) (1-8)	IG1	4	4.5 (1.9)	27	4.5 (1.8)	NR	4.6 (3.0)	29	4.8 (2.5)	NR	Adj MD (95% CI)=-0.01 (-1.21, 1.18), 0.98
	Caregiver + patient	Zarit-10 (0-40)	IG1	4	21.0 (9.0)	27	20.3 (8.8)	NR	21.3 (9.2)	29	20.6 (10.4)	NR	Adj MD (95% CI)=0.75 (-3.36, 4.85), 0.72
Gitlin, 2010[348] Fair	Caregiver	Zarit-12 (0-48)	IG1	4	21.2 (9.5)	117	19.0 (8.5)	NR	22.0 (9.6)	122	21.0 (9.3)	NR	MD (95% CI)=-1.37 (-2.75, -0.01), 0.05
	Caregiver	Zarit-12 (0-48)	IG1	6	21.2 (9.5)	114	19.1 (9.0)	NR	22.0 (9.6)	106	21.3 (9.8)	NR	MD (95% CI)=-1.61 (-3.13, -0.09), 0.04
Hebert, 2003[350] Fair	Caregiver	RMBPC (average burden) (0-4)	IG1	4	2.01 (0.75)	60	1.77 (0.74)	-0.28 (0.55)	2.18 (0.69)	56	2.07 (0.72)	-0.10 (0.60)	NR, 0.04
	Caregiver	Zarit-22 (0-88)	IG1	4	42.47 (14.63)	60	40.07 (14.84)	-2.40 (14.96)	41.44 (15.16)	56	41.25 (16.55)	0.09 (11.99)	NR, 0.39
Hepburn, 2005[351] Fair	Caregiver	Zarit-22 (0-88)	IG1	6	34.8 (12.5)	120	36.2 (12.2)	1.2 (8.1)	32.0 (13.7)	46	34.9 (14.5)	3.5 (7.9)	NR, 0.25
	Caregiver	Zarit-22 (0-88)	IG1	12	34.8 (12.5)	91	37.0 (13.9)	1.9 (10.8)	32.0 (13.7)	40	37.0 (12.7)	5.0 (10.5)	NR, 0.21
Kwok, 2013*[356] Fair	Caregiver	Zarit-22 (0-88)	IG1	3	37.4 (8.66)	18	35.6 (7.52)	-1.83 (5.26)	34.1 (13.3)	20	36.4 (11.4)	2.25 (7.09)	NR, 0.002
Martin-Carrasco, 2009[362] Fair	Caregiver	Zarit-22 (22-110)	IG1	4	62.0 (14.9)	4	56.6 (16.4)	NR	58.4 (15.9)	38	58.3 (16.7)	NR	NR, 0.6
	Caregiver	Zarit-22 (22-110)	IG1	10	62.0 (14.9)	44	54.0 (15.9)	-8.1 (17.3)	58.4 (15.9)	38	60.5 (16.6)	2.1 (16.5)	NR, 0.08
Martin-Carrasco, 2014*[361] Fair	Caregiver	Zarit-22 (0-88)	IG1	4	33.9 (14.5)	115	NR	-1.17 (12.3)	34.0 (14.4)	123	NR	-0.63 (12.0)	MDC (95% CI)=-0.55 (-3.64, 2.55), 0.73
Martin-Cook, 2005[363] Fair	Caregiver + patient	NPI-10 (1-114)	IG1	4	13.29 (13.90)	24	10.63 (2.53)‡	NR	12.48 (11.33)	23	10.41 (2.64)‡	NR	NS
Martindale-Adams, 2013*[364] Fair	Caregiver	RMBPC (total burden) (0-96)	IG1	3	21.0 (13.7)	77	17.7 (12.0)	NR	26.4 (18.0)	77	22.4 (16.2)	NR	NR
	Caregiver	RMBPC (total burden) (0-96)	IG1	6	21.0 (13.7)	77	17.0 (12.4)	NR	26.4 (18.0)	77	22.6 (17.2)	NR	NR

Appendix H Table 1. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Burden Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Caregiver	RMBPC (total burden) (0-96)	IG1	9	21.0 (13.7)	77	15.1 (10.7)	NR	26.4 (18.0)	77	19.0 (13.3)	NR	NR
	Caregiver	RMBPC (total burden) (0-96)	IG1	12	21.0 (13.7)	77	18.6 (14.1)	NR	26.4 (18.0)	77	21.7 (16.5)	NR	Cohen's D: 0.07, 0.875
	Caregiver	Zarit-12 (0-48)	IG1	6	16.4 (8.3)	77	15.6 (7.9)	NR	17.7 (9.1)	77	15.6 (9.3)	NR	NR
	Caregiver	Zarit-12 (0-48)	IG1	12	16.4 (8.3)	77	14.5 (6.6)	NR	17.7 (9.1)	77	15.3 (9.1)	NR	Cohen's D: 0.07, 0.708
Mittelman, 2004*[365] Fair	Family	MBPC (average) (NR)	IG1	48	22.3 (13.8)	203	NR	NR	24.8 (17.0)	203	NR	NR	logBeta (SE)=-1.86 (0.89), 0.0368
Ostwald, 1999[367] Fair	Caregiver + patient	RMBPC Disruptive behaviors (average burden) (0-32)	IG1	3	6.8 (6.3)	53	5.0 (5.4)	NR	5.2 (5.1)	31	4.4 (4.2)	NR	NR
	Caregiver + patient	RMBPC Disruptive behaviors (average burden) (0-32)	IG1	5	6.8 (6.3)	60	4.148 (4.358)	NR	5.2 (5.1)	34	5.790 (4.366)	NR	F statistic=5.734, 0.019
	Caregiver + patient	Zarit-22 (0-88)	IG1	3	56.2 (13.3)	50	56.8 (11.8)	NR	56.5 (15.9)	30	55.4 (15.9)	NR	NR
	Caregiver + patient	Zarit-22 (0-88)	IG1	5	56.2 (13.3)	60	53.9 (12.4)	NR	56.5 (15.9)	34	59.4 (5.6)	NR	NR, 0.05
Roberts, 1999[368] Fair	Caregiver	PAIS (NR)	IG1	12	42.2 (16.5)	29	42.9 (17.1)	NR	47.5 (21.7)	29	46.1 (23.5)	NR	NR, 0.55
Spaulding-Wilson, 2018*[370] Fair	Caregiver	CBI (0-96)	IG1	6	34.9 (15.3)	54	NR	NR	34.3 (12.2)	41	NR	NR	Beta (SE)=-0.448 (0.53), 0.397
Steffen, 2016*[371] Good	Caregiver	RMBPC (total burden) (0-96)	IG1	3	19.3 (0)	28	10.7 (1.4)	NR	19.3 (0)	38	14.5 (1.2)	NR	Cohen's D: 0.05, ≤0.05
	Caregiver	RMBPC (total burden) (0-96)	IG1	9	19.3 (0)	22	10.1 (1.8)	NR	19.3 (0)	30	13.3 (1.5)	NR	NR, 0.18
Teri, 2005[372] Fair	Caregiver	RMBPC (total burden) (0-96)	IG1	6	11.3 (3.9)	32	9.2 (4.6)	NR	10.5 (3.9)	34	9.1 (5.2)	NR	Adj MD (95% CI)=-3.2 (-6.1, -0.2),
Tremont, 2015*[373] Fair	Caregiver	RMBPC (total burden) (0-96)	IG1	6	22.98 (12.89)	133	20.04 (13.68)	NR	22.59 (13.94)	117	22.00 (12.82)	NR	NR, 0.16
	Caregiver	RMBPC Depressive behaviors (total burden) (0-36)	IG1	6	8.87 (7.06)	133	6.53 (6.36)	NR	7.96 (7.85)	117	7.97 (6.74)	NR	NR, 0.009

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	Caregiver	RMBPC Disruptive behaviors (total burden) (0-32)	IG1	6	5.92 (5.44)	133	5.81 (5.80)	NR	5.91 (4.84)	117	5.73 (5.20)	NR	NR, 0.909
	Caregiver	RMBPC Memory problems (total burden) (0-28)	IG1	6	8.25 (5.24)	133	7.72 (5.28)	NR	8.90 (5.82)	117	8.33 (5.50)	NR	NR, 0.955
	Caregiver	Zarit-22 (0-88)	IG1	6	38.61 (13.98)	133	35.95 (14.34)	NR	38.82 (14.63)	117	37.17 (13.93)	NR	NR, 0.485
Wang, 2011*[377] Fair	Caregiver + patient	FCBI (0-96)	IG1	6	68.2 (11.9)	40	55.2 (15.0)	NR	68.8 (16.7)	40	65.0 (18.1)	NR	NR, <0.001
Wright, 2001[381] Fair	Caregiver	Caregiving Hassle Scale (0-123)	IG1	3	27.5§ (NR)	68	23.4§ (NR)	NR	28.7§ (NR)	25	24.3§ (NR)	NR	NS
	Caregiver	Caregiving Hassle Scale (0-123)	IG1	6	27.5§ (NR)	68	24.0§ (NR)	NR	28.7§ (NR)	25	24.2§ (NR)	NR	NS
	Caregiver	Caregiving Hassle Scale (0-123)	IG1	12	27.5§ (NR)	68	21.9§ (NR)	NR	28.7§ (NR)	25	21.6§ (NR)	NR	NR, 0.98
Care/Case Management Interventions													
Callahan, 2006[383] Fair	Caregiver + patient	NPI-12 (0-60)	IG1	6	4.2 (5.6)	84	4.4 (6.4)	NR	6.5 (10.4)	69	5.7 (7.2)	NR	Adj MD (95% CI)=-0.1 (-2.0, 1.8), 0.92
	Caregiver + patient	NPI-12 (0-60)	IG1	12	4.2 (5.6)	84	3.5 (5.8)	NR	6.5 (10.4)	69	7.7 (8.7)	NR	Adj MD (95% CI)=-2.2 (-4.2, -0.2), 0.03
	Caregiver + patient	NPI-12 (0-60)	IG1	17	4.2 (5.6)	84	4.6 (6.3)	NR	6.5 (10.4)	69	7.4 (9.7)	NR	Adj MD (95% CI)=-1.0 (-3.0, 1.0), 0.33
Chien, 2008*[385] Fair	Family	FCBI (0-96)	IG1	6	68.1 (14.9)	44	56.7 (15.7)	NR	67.8 (15.7)	44	63.0 (15.1)	NR	NR
Chien, 2008*[385] Fair	Family	FCBI (0-96)	IG1	12	68.1 (14.9)	44	48.3 (13.9)	NR	67.8 (15.7)	44	65.9 (16.3)	NR	F statistic=7.1, <0.001
Chien, 2011*[384] Good	Caregiver + patient	FCBI (0-96)	IG1	12	68.0 (14.6)	46	48.1 (13.0)	NR	66.9 (13.7)	46	65.3 (15.3)	NR	MD (SE)=-17.2 (0.8), 0.01
	Caregiver + patient	FCBI (0-96)	IG1	18	68.0 (14.6)	45	45.5 (10.0)	NR	66.9 (13.7)	45	64.1 (11.4)	NR	MD (SE)=-18.6 (1.0), 0.01
Chu, 2000[386] Fair	Caregiver	RMBPC (total burden) (0-96)	IG1	3	15.6 (NR)	32	17.8 (NR)	NR	14.9 (NR)	31	18.8 (NR)	NR	NS
	Caregiver	RMBPC (total burden) (0-96)	IG1	6	15.6 (NR)	22	10.7 (NR)	NR	14.9 (NR)	26	21.1 (NR)	NR	NR, <0.05

Appendix H Table 1. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Burden Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)[†]	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Caregiver	RMBPC (total burden) (0-96)	IG1	10	15.6 (NR)	22	15.7 (NR)	NR	14.9 (NR)	26	20.2 (NR)	NR	NS
	Caregiver	RMBPC (total burden) (0-96)	IG1	13	15.6 (NR)	18	23.9 (NR)	NR	14.9 (NR)	19	21.4 (NR)	NR	NS
	Caregiver	RMBPC (total burden) (0-96)	IG1	17	15.6 (NR)	27	18.6 (NR)	NR	14.9 (NR)	22	17.2 (NR)	NR	NS
	Caregiver	Zarit-22 (0-88)	IG1	3	26.2 (NR)	32	26.0 (NR)	NR	26.2 (NR)	31	27.5 (NR)	NR	NS
	Caregiver	Zarit-22 (0-88)	IG1	6	26.2 (NR)	22	22.3 (NR)	NR	26.2 (NR)	26	33.5 (NR)	NR	NR, <0.05
	Caregiver	Zarit-22 (0-88)	IG1	10	26.2 (NR)	22	25.3 (NR)	NR	26.2 (NR)	20	30.0 (NR)	NR	NS
Chu, 2000[386] Fair	Caregiver	Zarit-22 (0-88)	IG1	13	26.2 (NR)	16	28.3 (NR)	NR	26.2 (NR)	19	33.9 (NR)	NR	NS
	Caregiver	Zarit-22 (0-88)	IG1	17	26.2 (NR)	27	27.1 (NR)	NR	26.2 (NR)	21	29.5 (NR)	NR	NS
Fortinsky, 2009[389] Fair	Caregiver + patient	Zarit-22 (0-88)	IG1	12	30.42 (NR)	44	26.18 (NR)	NR	36.02 (NR)	25	30.57 (NR)	NR	MD=0.73, NR
Jansen, 2011[390] Fair	Caregiver	SPPIC (0-9)	IG1	6	3.9 (NR)	54	3.8 (NR)	NR	3.3 (NR)	45	2.7 (NR)	NR	NS
	Caregiver	SPPIC (0-9)	IG1	12	3.9 (NR)	54	4.2 (NR)	NR	3.3 (NR)	45	3.3 (NR)	NR	F statistic=0.72, 0.49
Lam, 2010[391] Fair	Caregiver + patient	Zarit-22 (0-88)	IG1	4	33.2 (17.8)	57	NR	2.0[‖] (-7.0, 9.5)	32.3 (15.8)	42	NR	1.5[‖] (-7.0, 9.3)	NS
	Caregiver + patient	Zarit-22 (0-88)	IG1	12	33.2 (17.8)	53	NR	5.0[‖] (-10.5, 12.0)	32.3 (15.8)	39	NR	3.5[‖] (-9.3, 12.3)	NS
Mavandadi, 2017*[392] Fair	Caregiver + patient	NPI-10 (0-50)	IG1	6	10.04 (0.55)[‡]	25	6.74 (0.72)[‡]	NR	9.17 (0.58)[‡]	31	9.67 (0.69)[‡]	NR	Beta (SE)=-0.68 (0.26), 0.01
	Caregiver + patient	RMBPC (total burden) (0-96)	IG1	6	18.59 (0.83)[‡]	25	13.71 (1.07)[‡]	NR	18.21 (0.86)[‡]	31	18.03 (1.03)[‡]	NR	Beta (SE)=-0.80 (0.41), 0.05
	Caregiver + patient	Zarit-12 (0-48)	IG1	6	14.89 (10.04)	25	NR	NR	14.30 (9.17)	31	NR	NR	Beta (SE)=-0.05 (0.22), 0.82
Menn, 2012[394] Fair	Caregiver + patient	BSFC (0-72)	IG1	22	22.1 (NR)	53	27.8 (NR)	NR	23.6 (NR)	83	29.0 (NR)	NR	NS
	Caregiver + patient	BSFC (0-72)	IG2	22	24.5 (NR)	60	29.1 (NR)	NR	23.6 (NR)	83	29.0 (NR)	NR	NS

Appendix H Table 1. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Burden Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Samus, 2014*[395] Fair	Caregiver + patient	Zarit-12 (0-44)	IG1	18	14.18 (0.89)‡	106	13.90 (0.99)‡	NR	14.51 (0.67)‡	183	16.14 (0.79)‡	NR	MDC (95% CI)=-1.91 (-3.9, 0.5), 0.29
Thyrian, 2017*[396] Fair	Caregiver + patient	BIZA-D (NR)	IG1	12	-0.14 (2.62)	291	-0.13 (2.63)	NR	-0.07 (2.57)	116	0.40 (2.62)	NR	Beta (95% CI)=-0.50 (-1.09, 0.08), 0.045
Xiao, 2016*[398] Fair	Caregiver	NPI-10 (0-50)	IG1	6	10.8 (9.4)	31	6.5 (6.7)	NR	11.2 (9.3)	30	11.9 (11.7)	NR	NR
	Caregiver	NPI-10 (0-50)	IG1	12	10.8 (9.4)	31	6.3 (6.6)	NR	11.2 (9.3)	30	13.1 (11.9)	NR	F statistic=4.97, 0.01
Other Interventions													
Connell, 2009[400] Fair	Caregiver	RMBPC (total burden) (0-96)	IG1	6	14.7 (11.5)	74	12.9 (10.9)	NR	14.4 (9.1)	63	13.4 (10.0)	NR	NR, <0.05
	Caregiver	RMBPC (total burden) (0-96)	IG1	12	14.7 (11.5)	69	13.2 (12.8)	NR	14.4 (9.1)	61	13.4 (11.9)	NR	NS
Hirano, 2011[402] Fair	Caregiver	Zarit-22 (0-88)	IG1	3	32.9 (18.2)	17	NR	-5.2 (2.1)	38.5 (19.7)	14	NR	0.07 (0.5)	NR
King, 2002[403] Fair	Caregiver	RMBPC (total burden) (0-77)	IG1	12	24.6 (15.4)	45	23.6 (15.4)	NR	25.5 (10.3)	40	23.0 (12.1)	NR	NS
	Caregiver	SCB objective (0-25)	IG1	12	11.5 (3.7)	45	10.8 (3.6)	NR	12.6 (4.0)	40	11.8 (4.8)	NR	NR
	Caregiver	SCB subjective (25-100)	IG1	12	39.6 (9.4)	45	35.7 (7.5)	NR	43.7 (9.8)	40	40.9 (12.8)	NR	NR
Logiudice, 1999[405] Fair	Caregiver + patient	RMBPC (total burden) (0-96)	IG1	6	56.3 (58.0)	20	NR	2.52 (NR)	67.8 (45.0)	14	NR	6.82 (NR)	MDC=0.30, NR
	Caregiver + patient	RMBPC (total burden) (0-96)	IG1	12	56.3 (58.0)	15	NR	2.1 (NR)	67.8 (45.0)	12	NR	-6.29 (NR)	MDC=0.70, NR
	Caregiver + patient	Zarit-22 (0-88)	IG1	6	39.0 (8.7)	23	NR	0.16 (NR)	42.7 (10.3)	16	NR	4.21 (NR)	NR, 0.02
	Caregiver + patient	Zarit-22 (0-88)	IG1	12	39.0 (8.7)	16	NR	0.77 (NR)	42.7 (10.3)	14	NR	3.11 (NR)	NR, 0.4
Prick, 2015*[408] Fair	Caregiver + patient	RMBPC (total burden) (0-100)	IG1	3	13.48 (9.21)	57	13.06 (10.38)	NR	13.76 (8.40)	54	12.13 (8.55)	NR	Beta (95% CI)=0.00 (-0.29, 0.30), 0.98
	Caregiver + patient	RMBPC (total burden) (0-100)	IG1	6	13.48 (9.21)	57	15.98 (11.11)	NR	13.76 (8.40)	54	11.71 (9.25)	NR	Beta (95% CI)=0.08 (-

Appendix H Table 1. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Burden Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
													0.22, -0.37), 0.61
	Caregiver + patient	SPPIC (0-9)	IG1	3	5.53 (2.39)	57	5.67 (2.36)	NR	5.52 (2.37)	54	5.85 (2.13)	NR	Beta (95% CI)=-0.19 (-0.72, 0.34), 0.49
	Caregiver + patient	SPPIC (0-9)	IG1	6	5.53 (2.39)	57	5.69 (2.38)	NR	5.52 (2.37)	54	5.60 (2.13)	NR	Beta (95% CI)=-0.21 (-0.73, 0.31), 0.43
Winter, 2006[411] Fair	Caregiver	Zarit-22 (0-88)	IG1	6	33.7 (14.5)	53	31.66 (15.16)	NR	35.0 (15.1)	49	31.74 (17.29)	NR	MD=0.490, NR

* New study
† Higher values indicate better outcomes for all instruments
‡ Standard error
§ Least squares mean
‖ Median change (IQR)

Abbreviations: Adj MD = adjusted mean difference; BIZA-D = Berlin Inventory of Caregivers' Burden with Dementia; BL = baseline; CBI = Caregiver Burden Inventory; CG = control group; CI = confidence interval; FCBI = Family Caregiving Burden Inventory; FU = followup; IG = intervention group; Int arm = intervention arm; IQR = interquartile range; MD = mean difference; MDC = mean difference in change; mo. = months; NPI-10 = Neuropsychiatric Inventory-10 item; NPI-12 = Neuropsychiatric Inventory-12 item; NR = not reported; NS = not statistically significant; PAIS = Psychosocial Adjustment to Illness scale; RMBPC = Revised Memory and Behavior Checklist; SD = standard deviation; SE = standard error; SPPIC = Self-Perceived Pressure by Informal Care; Zarit-10 = Zarit Burden Interview-10 item; Zarit-22 = Zarit Burden Interview-22 item

Appendix H Table 2. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Mental Health Outcomes, by Intervention Type

Author, year Quality	Audience	Symptom (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Psychoeducation Interventions													
Barnes, 2018*[325] Fair	Caregiver	Anx (HADS-A, 0-21, ↓)	IG1	3	8.1 (NR)	27	7.8 (NR)	-0.3 (NR)	7.9 (NR)	25	8.4 (NR)	0.5 (NR)	NR, 0.100
	Caregiver	Dep (HADS-D, 0-21, ↓)	IG1	3	5.8 (NR)	27	5.9 (NR)	0.1 (NR)	5.4 (NR)	25	6.2 (NR)	0.8 (NR)	NR, 0.122
	Caregiver	Psych Health (HADS-T, 0-42, ↓)	IG1	3	13.9 (NR)	27	13.7 (NR)	-0.2 (NR)	13.3 (NR)	25	14.6 (NR)	1.3 (NR)	NR, 0.133
Belle, 2006[326] Fair	Caregiver	Dep (CES-D, D)	IG1	6	NA	293	37 (12.6)†	NR	NA	286	65 (22.7)†	NR	NR, 0.0014
Berwig, 2017*[327] Fair	Caregiver	Anx (PHQ-4-Anx subscale, 0.6, ↓)	IG1	6	2.2 (1.6)	41	NR	-0.342 (1.995)	1.8 (1.9)	40	NR	-0.025 (1.981)	ES=0.159, 0.476
	Caregiver	Anx (PHQ-4-Anx subscale, 0.6, ↓)	IG1	9	2.2 (1.6)	31	NR	-0.194 (1.815)	1.8 (1.9)	31	NR	0.548 (2.743)	ES=0.326, 0.239
	Caregiver	Dep (PHQ-4-Dep subscale, 0.6, ↓)	IG1	6	2.0 (1.4)	41	NR	-0.317 (1.439)	1.4 (1.5)	40	NR	0.075 (1.403)	ES=0.276, 0.218
	Caregiver	Dep (PHQ-4-Dep subscale, 0.6, ↓)	IG1	9	2.0 (1.4)	31	NR	-0.097 (1.446)	1.4 (1.5)	31	NR	0.129 (1.432)	ES=0.157, 0.214
Brennan, 1995[328] Fair	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	12	21.2 (8.1)	47	18.9 (11.0)	NR	15.6 (10.6)	49	15.7 (10.5)	NR	NR, 0.61
Bruvik, 2013*[329] Good	Caregiver + patient	Dep (GDS, 0-30, ↓)	IG1	12	7.3 (6.5)	93	7.3 (6.8)	NR	5.6 (5.5)	102	5.6 (6.0)	NR	NR, 0.8236
Burgio, 2003[330] Fair	Caregiver	Anx (STPI-Anx subscale, 10-40, ↓)	IG1 (Black)	6	21.68 (7.92)	25	19.16 (8.01)	NR	19.91 (7.17)	23	19.04 (6.79)	NR	NR
	Caregiver	Anx (STPI-Anx subscale, 10-40, ↓)	IG1 (White)	6	22.17 (5.93)	36	22.61 (7.64)	NR	18.03 (6.24)	34	18.12 (7.36)	NR	NR
	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	6	15.7 (9.4)	60	11.4 (1.2)	NR	11.4 (9.9)	61	12.1 (9.9)	NR	NR, 0.35
Chang, 1999[331] Fair	Caregiver	Anx (BSI-A, 0-24, ↓)	IG1	3	0.68 (0.55)	31	0.57 (0.58)	NR	0.91 (0.63)	34	0.78 (0.74)	NR	NR
	Caregiver	Dep (BSI-D, 0-4, ↓)	IG1	3	0.73 (0.66)	31	0.60 (0.71)	NR	0.74 (0.74)	34	0.95 (0.85)	NR	NR
Chu, 2011[332] Fair	Caregiver	Dep (BDI-II, 0-63, ↓)	IG1	3	9.3 (NR)	30	5.77 (NR)	NR	11.36 (NR)	30	10.53 (NR)	NR	NR, 0.05
	Caregiver	Dep (BDI-II, 0-63, ↓)	IG1	4	9.3 (NR)	30	5.31 (NR)	NR	11.36 (NR)	30	10.96 (NR)	NR	NR, <0.01
Coon, 2003[333] Fair	Caregiver	Dep (MAACL Dep subscale, NR, ↓)	IG1	6	17.8 (1.4)	45	15.4 (1.3)	NR	14.6 (1.3)	44	16.5 (1.3)	NR	NR, NR
Coon, 2003[333] Fair	Caregiver	Dep (MAACL Dep subscale, NR, ↓)	IG2	6	16.4 (1.3)	41	15.0 (1.3)	NR	14.6 (1.3)	44	16.5 (1.3)	NR	NR, NR

Appendix H Table 2. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Mental Health Outcomes, by Intervention Type

Author, year Quality	Audience	Symptom (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Cristancho-Lacroix, 2015*[334] Fair	Caregiver	Dep (BDI-II, 0-63, ↓)	IG1	3	11.2 (10.1)	25	11.5 (9.2)	0.3 (4.6)	9.0 (7.4)	24	8.9 (6.5)	-0.1 (2.7)	MDC (95% CI)=NR (NR, NR), 0.56
	Caregiver	Dep (BDI-II, 0-63, ↓)	IG1	6	11.2 (10.1)	25	12.4 (11.6)	NR	9.0 (7.4)	24	8.8 (7.2)	NR	NS
	Caregiver	Perc Stress (Cohen PSS, 0-56, ↓)	IG1	3	24.2 (9.0)	25	23.7 (9.2)	-0.5 (8.0)	24.5 (6.7)	24	23.8 (6.2)	-0.7 (4.5)	MDC (95% CI)=NR (NR, NR), 0.98
	Caregiver	Perc Stress (Cohen PSS, 0-56, ↓)	IG1	6	24.2 (9.0)	25	25.0 (9.9)	NR	24.5 (6.7)	24	23.8 (6.9)	NR	NS
De Rotrou, 2011[335] Fair	Caregiver	Dep (MADRS, 0-60, ↓)	IG1	3	9.0 (7.5)	63	8.2 (7.5)	NR	10.2 (9.2)	64	10.1 (9.9)	NR	NR, 0.21
	Caregiver	Dep (MADRS, 0-60, ↓)	IG1	6	9.0 (7.5)	56	8.9 (7.8)	NR	10.2 (9.2)	57	11.4 (10.3)	NR	NR, 0.14
Finkel, 2007[338] Fair	Caregiver	Dep (CES-D-10, 0-30, ↓)	IG1	6	7.2 (NR)	17	4.3 (NR)	NR	7.2 (NR)	19	6.0 (NR)	NR	Cohen's d=0.42, 0.099
Gallagher-Thompson, 2003[340] Fair	Caregiver	Dep (CES-D, 0-60, ↓)	IG1 (Hispanic)	6	16.74 (12.53)	38	15.27 (1.66)	NR	26.67 (14.75)	17	17.10 (2.55)	NR	NR
	Caregiver	Dep (CES-D, 0-60, ↓)	IG1 (White)	6	18.84 (11.48)	53	13.50 (1.08)	NR	17.13 (13.50)	24	15.44 (1.60)	NR	NR
Gallagher-Thompson, 2008[341] Fair	Caregiver	Dep (CES-D, 0-60, ↓)	IG1 (Hispanic)	6	14.83 (12.47)	47	10.26 (9.98)	NR	15.64 (13.60)	42	12.83 (10.31)	NR	NR
	Caregiver	Dep (CES-D, 0-60, ↓)	IG1 (White)	6	15.14 (10.46)	50	11.86 (9.90)	NR	13.39 (9.42)	45	12.82 (9.59)	NR	NR
	Caregiver	Perc Stress (Cohen PSS, 0-40, ↓)	IG1 (Hispanic)	6	18.02 (7.91)	47	15.23 (7.24)	NR	17.00 (7.79)	42	16.14 (6.97)	NR	NR
Gallagher-Thompson, 2008[341] Fair	Caregiver	Perc Stress (Cohen PSS, 0-40, ↓)	IG1 (White)	6	18.92 (6.98)	50	15.97 (6.49)	NR	18.16 (6.67)	45	17.04 (6.17)	NR	NR
Gallagher-Thompson, 2010*[342] Good	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	4	13.03 (11.85)	36	10.78 (8.41)	NR	14.74 (12.51)	34	13.94 (10.31)	NR	Beta=-0.118, 0.164
Garand, 2014*[343] Fair	Caregiver	Anx (STAI-State, 20-80, ↓)	IG1 (AD patient)	3	31.3 (2.9)‡	13	27.1 (3.1)‡	NR	32.3 (2.7)‡	17	39.5 (2.6)‡	NR	NR
	Caregiver	Anx (STAI-State, 20-80, ↓)	IG1 (AD patient)	6	31.3 (2.9)‡	13	27.1 (2.3)‡	NR	32.3 (2.7)‡	17	43.3 (2.6)‡	NR	NR

Appendix H Table 2. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Mental Health Outcomes, by Intervention Type

Author, year Quality	Audience	Symptom (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Caregiver	Anx (STAI-State, 20-80, ↓)	IG1 (AD patient)	12	31.3 (2.9)‡	13	32.5 (3.0)‡	NR	32.3 (2.7)‡	17	40.5 (2.8)‡	NR	NR
	Caregiver	Anx (STAI-State, 20-80, ↓)	IG1 (MCI patient)	3	26.3 (2.2)‡	23	27.3 (2.2)‡	NR	27.1 (2.7)‡	20	28.2 (2.1)‡	NR	NR
	Caregiver	Anx (STAI-State, 20-80, ↓)	IG1 (MCI patient)	6	26.3 (2.2)‡	23	26.0 (2.0)‡	NR	27.1 (2.7)‡	20	27.3 (2.4)‡	NR	NR
	Caregiver	Anx (STAI-State, 20-80, ↓)	IG1 (MCI patient)	12	26.3 (2.2)‡	23	28.5 (2.2)‡	NR	27.1 (2.7)‡	20	29.9 (2.3)‡	NR	NR
	Caregiver	Dep (CES-D, 0-60, ↓)	IG1 (AD patient)	3	13.3 (1.5)‡	13	10.8 (0.7)‡	NR	16.4 (2.5)‡	17	18.1 (4.0)‡	NR	NR
	Caregiver	Dep (CES-D, 0-60, ↓)	IG1 (AD patient)	6	13.3 (1.5)‡	13	7.4 (0.6)‡	NR	16.4 (2.5)‡	17	19.4 (3.9)‡	NR	NR
Garand, 2014*[343] Fair	Caregiver	Dep (CES-D, 0-60, ↓)	IG1 (AD patient)	12	13.3 (1.5)‡	13	7.9 (1.7)‡	NR	16.4 (2.5)‡	17	16.6 (2.0)‡	NR	NR
	Caregiver	Dep (CES-D, 0-60, ↓)	IG1 (MCI patient)	3	6.1 (0.4)‡	23	6.6 (0.4)‡	NR	7.1 (0.6)‡	20	8.0 (0.4)‡	NR	NR
	Caregiver	Dep (CES-D, 0-60, ↓)	IG1 (MCI patient)	6	6.1 (0.4)‡	23	6.3 (0.5)‡	NR	7.1 (0.6)‡	20	8.1 (2.9)‡	NR	NR
	Caregiver	Dep (CES-D, 0-60, ↓)	IG1 (MCI patient)	12	6.1 (0.4)‡	23	4.9 (0.3)‡	NR	7.1 (0.6)‡	20	11.5 (1.8)‡	NR	NR
Gaugler, 2013*[344] Fair	Whole family	Dep (GDS, 0-30, ↓)	IG1	36	6.11 (5.39)	54	NR	NR	5.48 (4.59)	53	NR	NR	Beta (SE)= 0.07 (0.51), NS
Gitlin, 2003[347] Fair	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	6	15.25 (12.17)	116	15.06 (0.66)	NR	14.85 (10.73)	117	15.05 (0.66)	NR	NR, 0.99
Gitlin, 2008[346] Fair	Caregiver + patient	Dep (CES-D, 0-60, ↓)	IG1	4	14.6 (11.0)	27	13.1 (9.4)	NR	13.2 (9.6)	29	14.3 (10.2)	NR	Adj MD (95% CI)=-0.74 (-4.31, 2.82), 0.68
Gitlin, 2010[348] Fair	Caregiver	Dep (CES-D, D)	IG1	4	NA	117	62 (53.0)§	NR	NA	122	83 (68.0)§	NR	NR, 0.02

Appendix H Table 2. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Mental Health Outcomes, by Intervention Type

Author, year Quality	Audience	Symptom (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Graff, 2006[349] Fair	Caregiver + patient	Dep (CES-D, 0-60, ↓)	IG1	3	11.7 (8.3)	67	5.4 (4.5)	NR	11.4 (7.2)	65	13.1 (9.1)	NR	Adj MD (95% CI)=-8.4 (-11.0, -5.8), <0.0001
	Caregiver + patient	Psych Health (GHQ-12, 0-36, ↓)	IG1	3	12.0 (4.9)	67	7.1 (3.5)	NR	11.3 (4.0)	65	12.1 (5.0)	NR	Adj MD (95% CI)=-4.9 (-6.6, -3.3), <0.0001
Hebert, 2003[350] Fair	Caregiver	Anx (STAI-State, 20-80, ↓)	IG1	4	41.01 (12.96)	60	39.75 (13.24)	-1.27 (16.47)	45.46 (14.82)	56	43.17 (14.02)	-1.64 (14.49)	NR, 0.39
Hebert, 2003[350] Fair	Caregiver	Psych Health (PSI, 14-56, ↓)	IG1	4	26.17 (6.94)	60	25.01 (6.92)	-1.16 (7.98)	26.45 (8.12)	56	26.89 (8.16)	0.65 (6.03)	NR, 0.13
Joling, 2012[352] Fair	Whole family	Anx (HADS-A, 0-21, ↓)	IG1	6	5.6 (NR)	96	5.6 (NR)	NR	5.3 (NR)	96	5.7 (NR)	NR	NR
	Whole family	Anx (HADS-A, 0-21, ↓)	IG1	12	5.6 (NR)	96	5.5 (NR)	NR	5.3 (NR)	96	5.8 (NR)	NR	ES (95% CI)=-0.6 (-1.6, 0.5), 0.3
	Whole family	Anx (HADS-A, D)	IG1	12	NA	96	28 (29.2)[‖]	NR	NA	96	27 (28.1)[‖]	NR	HR (95% CI)=0.89 (0.51, 1.56)
	Whole family	Dep (CES-D, 0-60, ↓)	IG1	6	11.4 (NR)	96	12.4 (NR)	NR	11.9 (NR)	96	13.0 (NR)	NR	NR
	Whole family	Dep (CES-D, 0-60, ↓)	IG1	12	11.4 (NR)	96	12.9 (NR)	NR	11.9 (NR)	96	14.8 (NR)	NR	ES (95% CI)=-1.4 (-3.9, 1.1), 0.27
	Whole family	Dep (CES-D, D)	IG1	12	NA	96	28 (29.2)[¶]	NR	NA	96	19 (19.8)[¶]	NR	IRR (95% CI)=1.21 (0.80, 1.84), NR
Judge, 2013*[353] Fair	Caregiver + patient	Dep (CES-D, 0-20, ↓)	IG1	3	4.47 (3.60)	59	3.75 (3.09)	NR	4.58 (3.63)	59	4.64 (3.19)	NR	Beta=-0.17, 0.04
Kurz, 2010[355] Fair	Caregiver	Dep (CES-D, D)	IG1	6	NA	55	NR	NR	NA	53	NR	NR	OR (95% CI)=0.15 (0.04, 0.65), <0.013[#]
Livingston, 2013*[358] Good	Caregiver	Anx (HADS-A, 0-21, ↓)	IG1	4	8.1 (4.4)	150	7.5 (4.2)	NR	9.3 (4.3)	75	8.6 (4.2)	NR	NR
	Caregiver	Anx (HADS-A, 0-21, ↓)	IG1	8	8.1 (4.4)	133	7.6 (4.4)	NR	9.3 (4.3)	71	8.8 (4.4)	NR	Adj MD (95% CI)=-0.91 (-1.76, -0.07), NR
Livingston, 2013*[358] Good	Caregiver	Anx (HADS-A, 0-21, ↓)	IG1	12	8.1 (4.4)	138	7.5 (4.4)	NR	9.3 (4.3)	67	8.8 (5.1)	NR	NR
	Caregiver	Anx (HADS-A, 0-21, ↓)	IG1	24	8.1 (4.4)	132	8.1 (4.9)	NR	9.3 (4.3)	64	9.2 (5.3)	NR	Adj MD (95% CI)=-1.16 (-

Appendix H Table 2. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Mental Health Outcomes, by Intervention Type

Author, year Quality	Audience	Symptom (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
													2.15, -0.18), NR
	Caregiver	Anx (HADS-A, D)	IG1	4	85 (49.4)**	150	54 (36.0)**	NR	48 (55.2)**	75	36 (48.0)**	NR	NR
	Caregiver	Anx (HADS-A, D)	IG1	8	85 (49.4)**	133	53 (39.8)**	NR	48 (55.2)**	71	33 (46.5)**	NR	OR (95% CI)=0.30 (0.08, 1.05), NR
	Caregiver	Anx (HADS-A, D)	IG1	12	85 (49.4)**	138	54 (39.1)**	NR	48 (55.2)**	67	33 (49.3)**	NR	NR
	Caregiver	Anx (HADS-A, D)	IG1	24	85 (49.4)**	132	57 (43.2)**	NR	48 (55.2)**	64	32 (50.0)**	NR	OR (95% CI)=0.57 (0.26, 1.24), NR
	Caregiver	Dep (HADS-D, 0-21, ↓)	IG1	4	5.4 (3.8)	150	4.9 (3.9)	NR	5.5 (3.9)	75	5.7 (4.0)	NR	NR
	Caregiver	Dep (HADS-D, 0-21, ↓)	IG1	8	5.4 (3.8)	133	5.2 (4.0)	NR	5.5 (3.9)	71	6.1 (4.2)	NR	Adj MD (95% CI)=-0.91 (-1.71, -0.10), NR
	Caregiver	Dep (HADS-D, 0-21, ↓)	IG1	12	5.4 (3.8)	138	5.0 (4.2)	NR	5.5 (3.9)	67	5.9 (4.3)	NR	NR
	Caregiver	Dep (HADS-D, 0-21, ↓)	IG1	24	5.4 (3.8)	132	5.5 (4.2)	NR	5.5 (3.9)	64	6.3 (4.9)	NR	Adj MD (95% CI)=-1.45 (-2.32, -0.57), NR
	Caregiver	Dep (HADS-D, D)	IG1	4	36 (20.9)††	150	25 (16.7)††	NR	17 (19.5)††	75	18 (24.0)††	NR	NR
	Caregiver	Dep (HADS-D, D)	IG1	8	36 (20.9)††	133	28 (21.1)††	NR	17 (19.5)††	71	23 (32.4)††	NR	OR (95% CI)=0.24 (0.07, 0.76), NR
Livingston, 2013*[358] Good	Caregiver	Dep (HADS-D, D)	IG1	12	36 (20.9)††	138	24 (17.4)††	NR	17 (19.5)††	67	18 (26.9)††	NR	NR
	Caregiver	Dep (HADS-D, D)	IG1	24	36 (20.9)††	132	30 (22.7)††	NR	17 (19.5)††	64	19 (29.7)††	NR	OR (95% CI)=0.14 (0.04, 0.53), NR
	Caregiver	Psych Health (HADS-T, 0-42, ↓)	IG1	4	13.5 (7.3)	150	12.4 (7.4)	NR	14.8 (7.4)	75	14.3 (7.4)	NR	NR
	Caregiver	Psych Health (HADS-T, 0-42, ↓)	IG1	8	13.5 (7.3)	133	12.9 (7.9)	NR	14.8 (7.4)	71	14.9 (8.0)	NR	Adj MD (95% CI)=-1.80 (-3.29, -0.31), 0.02
	Caregiver	Psych Health (HADS-T, 0-42, ↓)	IG1	12	13.5 (7.3)	138	12.5 (7.9)	NR	14.8 (7.4)	64	14.6 (8.9)	NR	NR

Appendix H Table 2. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Mental Health Outcomes, by Intervention Type

Author, year Quality	Audience	Symptom (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Caregiver	Psych Health (HADS-T, 0-42, ↓)	IG1	24	13.5 (7.3)	132	13.6 (8.3)	NR	14.8 (7.4)	64	15.5 (9.5)	NR	Adj MD (95% CI)=-2.58 (-4.26, -0.90), NR
	Caregiver	Psych Health (HSQ-12, 0-100, ↑)	IG1	4	58.3 (22.4)	144	62.7 (20.8)	NR	58.2 (21.7)	72	58.4 (18.0)	NR	NR
	Caregiver	Psych Health (HSQ-12, 0-100, ↑)	IG1	8	58.3 (22.4)	122	58.6 (22.0)	NR	58.2 (21.7)	66	58.2 (19.2)	NR	Adj MD (95% CI)=4.09 (0.34, 7.83), NR
	Caregiver	Psych Health (HSQ-12, 0-100, ↑)	IG1	12	58.3 (22.4)	121	61.9 (20.6)	NR	58.2 (21.7)	61	56.2 (22.5)	NR	NR
	Caregiver	Psych Health (HSQ-12, 0-100, ↑)	IG1	24	58.3 (22.4)	113	60.2 (19.8)	NR	58.2 (21.7)	55	55.0 (21.2)	NR	Adj MD (95% CI)=7.47 (2.87, 12.08),
Losada, 2010[359] Fair	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	3	19.5 (12.7)	68	14.9 (9.7)	NR	17.6 (12.7)	50	17.0 (12.0)	NR	Adj MD (SD)=-3.2 (NR), 0.03
Mariott, 2000[360] Fair	Caregiver	Dep (BDI, 0-63, ↓)	IG1	8	11.5 (9.5)	13	7.2 (7.5)	NR	9.9 (5.5)	14	10.9 (5.6)	NR	NR, <0.01
	Caregiver	Dep (BDI, 0-63, ↓)	IG1	12	11.5 (9.5)	13	6.3 (5.7)	NR	9.9 (5.5)	14	11.1 (6.4)	NR	NR, 0.001
	Caregiver	Psych Health (GHQ-28, 0-84, ↓)	IG1	8	9.5 (4.8)	13	5.1 (5.5)	NR	9.6 (3.8)	14	12.4 (6.4)	NR	NR, <0.05
	Caregiver	Psych Health (GHQ-28, 0-84, ↓)	IG1	12	9.5 (4.8)	13	3.2 (4.2)	NR	9.6 (3.8)	14	10.7 (5.5)	NR	NR, <0.05
Martin-Carrasco, 2009[362] Fair	Caregiver	Psych Health (GHQ-28, 0-84, ↓)	IG1	4	8.8 (7.5)	44	4.7 (7.2)	NR	6.8 (5.5)	38	6.3 (6.6)	NR	NR, 0.03
	Caregiver	Psych Health (GHQ-28, 0-84, ↓)	IG1	10	8.8 (7.5)	44	2.2 (4.0)	NR	6.8 (5.5)	38	7.8 (7.6)	NR	NR, 0.0004
Martin-Carrasco, 2014*[361] Fair	Caregiver	Psych Health (GHQ-28, 0-84, ↓)	IG1	4	28.2 (12.5)	115	NR	-4.76 (12.6)	27.7 (12.7)	123	NR	-2.42 (10.3)	MDC (95% CI)=-2.34 (-5.27, 0.59), NS
Martin-Cook, 2005[363] Fair	Caregiver + patient	Dep (GDS-15, 0-15, ↓)	IG1	4	1.79 (1.56)	23	1.58 (0.46)	NR	3.00 (3.26)	24	2.68 (0.48)	NR	NR
Martindale-Adams, 2013*[364] Fair	Caregiver	Dep (CES-D-10, 0-30, ↓)	IG1	6	10.8 (6.2)	77	10.0 (6.5)	NR	10.4 (6.8)	77	10.2 (7.1)	NR	NR
	Caregiver	Dep (CES-D-10, 0-30, ↓)	IG1	12	10.8 (6.2)	77	9.4 (5.7)	NR	10.4 (6.8)	77	9.4 (6.6)	NR	Cohen's d=0.04, 0.802

Appendix H Table 2. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Mental Health Outcomes, by Intervention Type

Author, year Quality	Audience	Symptom (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Mittelman, 2004*[365] Fair	Whole family	Dep (GDS, 0-30, ↓)	IG1	12	8.9 (5.7)	203	NR	-1.1 (5.0)	10.6 (7.2)	203	NR	0.3 (6.0)	logBeta (SE)= -1.41 (0.409), 0.006
	Whole family	Dep (GDS, 0-30, ↓)	IG1	60	8.9 (5.7)	203	NR	NR	10.6 (7.2)	203	NR	NR	Beta (SE)= -1.047 (0.473), 0.03
	Whole family	Dep (GDS, D)	IG1	12	81 (39.9)‡‡	203	60 (29.6)‡‡	NR	93 (45.8)‡‡	203	92 (45.3)‡‡	NR	NR
Mittelman, 2004*[365] Fair	Whole family	Dep (GDS, D)	IG1	36	81 (39.9)	203	53 (26.1)	NR	93 (45.8)	203	65 (32.0)	NR	NR
	Whole family	Dep (GDS, D)	IG1	60	81 (39.9)	203	55 (27.1)	NR	93 (45.8)	203	61 (30.0)	NR	NR
Nunez-Naveira, 2016*[366] Fair	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	3	19.40 (9.03)	30	17.03 (7.07)	NR	21.42 (8.64)	31	20.77 (9.02)	NR	NR
Ostwald, 1999[367] Fair	Caregiver + patient	Dep (CES-D, 0-60, ↓)	IG1	3	13.1 (8.2)	51	17.2 (4.1)	NR	14.7 (7.6)	30	18.0 (4.8)	NR	NR, NR
	Caregiver + patient	Dep (CES-D, 0-60, ↓)	IG1	5	13.1 (8.2)	60	12.0 (7.7)	NR	14.7 (7.6)	34	16.1 (9.1)	NR	NR, 0.04
Spaulding-Wilson, 2018*[370] Fair	Caregiver	Anx (BAI, 0-63, ↓)	IG1	6	8.1 (8.0)	54	NR	NR	7.7 (7.2)	41	NR	NR	Beta (SE)=-0.154 (0.39), 0.693
	Caregiver	Dep (BDI-II, 0-63, ↓)	IG1	6	11.8 (7.7)	54	NR	NR	11.7 (7.1)	41	NR	NR	Beta (SE)=-0.414 (0.37), 0.269
	Caregiver	Perc Stress (Cohen PSS, 0-48, ↓)	IG1	6	16.0 (6.5)	54	NR	NR	16.3 (5.6)	41	NR	NR	Beta (SE)=-0.716 (0.28), 0.010
Schoenmakers, 2010[369]	Caregiver	Dep (BDI, D)	IG1	NR	NA	23	NR	NR	NR	23	NR	NR	OR (95% CI)=0.16 (0.03, 0.86), NR§§
Steffen, 2016*[371] Good	Caregiver	Anx (MAACL Anx, 0-21, ↓)	IG1	3	4.8 (2.3)	28	3.5 (2.2)	NR	4.6 (2.3)	38	5.0 (2.7)	NR	Cohen's d=0.63, ≤0.05
	Caregiver	Anx (MAACL Anx, 0-21, ↓)	IG1	9	4.8 (2.3)	22	4.4 (2.6)	NR	4.6 (2.3)	30	4.2 (2.6)	NR	NR
	Caregiver	Dep (BDI-II, 0-63, ↓)	IG1	3	15.4 (0)	28	9.8 (1.3)	NR	15.4 (0)	38	13.2 (1.1)	NR	Cohen's d=0.50, ≤0.05
	Caregiver	Dep (BDI-II, D)	IG1	3	NA	28	20 (71.4)‖‖	NR	NA	38	16 (42.1)‖‖	NR	NR, ≤0.05
	Caregiver	Dep (BDI-II, 0-63, ↓)	IG1	9	15.4 (0)	22	10.3 (1.3)	NR	15.4 (0)	30	9.4 (1.1)	NR	NR, 0.61

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Author, year Quality	Audience	Symptom (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Caregiver	Psych Health (NAS, 10-50, ↓)	IG1	9	24.5 (6.9)	22	20.1 (7.3)	NR	24.1 (7.3)	30	21.7 (7.6)	NR	NR, 0.89
	Caregiver	Psych Health (NAS, 10-50, ↓)	IG1	3	24.5 (6.9)	28	17.6 (4.4)	NR	24.1 (7.3)	38	22.0 (7.0)	NR	Cohen's d=0.66, ≤0.05
Teri, 2005[372] Fair	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	6	14.8 (9.1)	32	12.5 (7.7)	NR	13.2 (8.5)	34	15.8 (10.5)	NR	Adj MD (95% CI)=-2.3 (-6.0, 0.0),
	Caregiver	Dep (HDRS, 0-52, ↓)	IG1	6	6.9 (4.1)	32	6.7 (3.9)	NR	7.6 (5.0)	34	8.5 (5.7)	NR	Adj MD (95% CI)=-1.2 (-2.4, -0.0),
Tremont, 2015*[373] Fair	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	6	17.04 (10.22)	133	14.15 (10.00)	NR	15.19 (9.98)	117	15.62 (10.18)	NR	NR, 0.003
Ulstein, 2007[374] Fair	Caregiver	Perc Stress (RSS, 0-60, ↓)	IG1	4	22.0 (10.3)	87	NR	-0.8 (-2.6, 1.0)¶¶	23.2 (10.8)	84	NR	-0.7 (-2.4, 0.9)¶¶	MDC (95% CI)=-0.1 (-2.5, 2.3), 0.94
	Caregiver	Perc Stress (RSS, 0-60, ↓)	IG1	12	22.0 (10.3)	87	NR	-2.4 (-4.7, -0.19)¶¶	23.2 (10.8)	84	NR	-1.2 (-3.2, 0.8)¶¶	MDC (95% CI)=-1.2 (-4.2, 1.8), 0.42
Voigt-Radloff, 2011[375] Fair	Caregiver + patient	Dep (CES-D, 0-60, ↓)	IG1	6	12.1 (7.7)	52	10.0 (7.9)	NR	11.3 (5.9)	46	10.0 (6.9)	NR	MD (95% CI)=0.0 (-3.0, 3.0), NS
	Caregiver + patient	Dep (CES-D, 0-60, ↓)	IG1	12	12.1 (7.7)	52	14.3 (10.3)	NR	11.3 (5.9)	46	12.9 (7.7)	NR	MD (95% CI)=-1.4 (-5.1, 2.3), NS
Waldorff, 2012[376] Good	Caregiver + patient	Dep (GDS, 0-30, ↓)	IG1	6	4.74 (5.16)	141	4.97 (5.06)	0.43 (3.51)	4.71 (5.02)	150	5.38 (5.77)	0.81 (3.91)	MDC (95% CI)=-0.39 (-0.72, -0.07), 0.02
	Caregiver + patient	Dep (GDS, 0-30, ↓)	IG1	12	4.74 (5.16)	128	5.64 (5.45)	1.16 (4.59)	4.71 (5.02)	143	4.82 (5.70)	0.20 (4.27)	MDC (95% CI)=0.91 (-0.21, 2.03), 0.11
	Caregiver + patient	Dep (GDS, 0-30, ↓)	IG1	36	4.74 (5.16)	163	5.83 (NR)	0.47 (-0.58, 1.52)¶¶	4.71 (5.02)	167	4.98 (NR)	-0.33 (-1.39, 0.72)¶¶	NR, 0.29
Williams, 2010[378] Fair	Caregiver	Anx (STAI-Trait, 20-80, ↓)	IG1	3	41.6 (10.3)	50	37.0 (NR)	NR	38.4 (11.1)	53	38.8 (NR)	NR	NS
	Caregiver	Anx (STAI-Trait, 20-80, ↓)	IG1	6	41.6 (10.3)	48	35.1 (NR)	NR	38.4 (11.1)	51	38.7 (NR)	NR	NS

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Author, year Quality	Audience	Symptom (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	3	18.7 (10.6)	50	12.9 (NR)	NR	14.4 (9.6)	53	14.5 (NR)	NR	NS
Williams, 2010[378] Fair	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	6	18.7 (10.6)	48	11.8 (NR)	NR	14.4 (9.6)	51	15.4 (NR)	NR	NS
	Caregiver	Perc Stress (Cohen PSS, 0-40, ↓)	IG1	3	21.5 (6.7)	50	16.5 (NR)	NR	19.1 (7.2)	53	17.8 (NR)	NR	NS
	Caregiver	Perc Stress (Cohen PSS, 0-40, ↓)	IG1	6	21.5 (6.7)	48	15.4 (NR)	NR	19.1 (7.2)	51	18.1 (NR)	NR	NS
Wilz, 2016*[379] Fair	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	3	16.89 (9.14)	102	15.12 (10.08)	NR	18.51 (8.79)	44	17.52 (9.96)	NR	MD (95% CI)=-0.99 (-4.05, 2.05), 0.815
	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	6	16.89 (9.14)	98	14.56 (9.61)	NR	18.51 (8.79)	39	17.33 (11.37)	NR	MD (95% CI)=0.06 (-5.09, 1.92), 0.624
Wilz, 2018*[380] Good	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	6	21.73 (9.66)	139	18.94 (9.61)	NR	23.27 (9.54)	134	20.92 (9.16)	NR	MD=-0.228, 0.043
	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	12	21.73 (9.66)	139	19.08 (10.12)	NR	23.27 (9.54)	134	20.10 (10.57)	NR	MD=-0.175, 0.180
Wright, 2001[381] Fair	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	3	13.1[##] (NR)	68	11.7[##] (NR)	NR	9.7[##] (NR)	25	7.6[##] (NR)	NR	NS
	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	6	13.1[##] (NR)	68	11.4[##] (NR)	NR	9.7[##] (NR)	25	6.7[##] (NR)	NR	NS
	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	12	13.1[##] (NR)	68	10.6[##] (NR)	NR	9.7[##] (NR)	25	8.3[##] (NR)	NR	NR, 0.94
Care/Case Management Interventions													
Bass, 2003[382] Fair	Caregiver + patient	Dep (CES-D, 0-20, ↓)	IG1	12	0.57 (0.40)	94	0.60 (0.39)	NR	0.62 (0.45)	63	0.76 (0.47)	NR	NR, ≤0.05
Callahan, 2006[383] Fair	Caregiver + patient	Dep (PHQ-9, 0-27)	IG1	6	3.8 (5.1)	84	3.6 (5.0)	NR	4.4 (5.6)	69	4.3 (5.1)	NR	Adj MD (95% CI)=-0.5 (-1.8, 0.9), 0.50
	Caregiver + patient	Dep (PHQ-9, 0-27)	IG1	12	3.8 (5.1)	84	3.1 (3.9)	NR	4.4 (5.6)	69	4.6 (5.6)	NR	Adj MD (95% CI)=-0.9 (-2.2, 0.5), 0.21
Callahan, 2006[383] Fair	Caregiver + patient	Dep (PHQ-9, 0-27)	IG1	17	3.8 (5.1)	84	3.1 (4.5)	NR	4.4 (5.6)	69	5.2 (5.3)	NR	Adj MD (95% CI)=-1.6 (-3.0, -0.2), 0.02

Appendix H Table 2. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Mental Health Outcomes, by Intervention Type

Author, year Quality	Audience	Symptom (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Fortinsky, 2009[389] Fair	Caregiver + patient	Dep (CES-D, 0-60, ↓)	IG1	12	12.1 (NR)	44	9.8 (NR)	NR	15.1 (NR)	25	15.0 (NR)	NR	NR, 0.41
Jansen, 2011[390] Fair	Caregiver + patient	Dep (CES-D, 0-60, ↓)	IG1	6	10.6 (NR)	54	11.9 (NR)	NR	11.2 (NR)	45	9.7 (NR)	NR	NS
	Caregiver + patient	Dep (CES-D, 0-60, ↓)	IG1	12	10.6 (NR)	54	11.2 (NR)	NR	11.2 (NR)	45	11.2 (NR)	NR	F=1.80, 0.17
Lam, 2010[391] Fair	Caregiver + patient	Psych Health (GHQ-28, 0-84, ↓)	IG1	4	13.1 (5.4)	57	NR	0.0 (-2.5, 3.0)***	14.2 (6.6)	42	NR	1.0 (-4.0, 4.0)***	NS
Lam, 2010[391] Fair	Caregiver + patient	Psych Health (GHQ-28, 0-84, ↓)	IG1	12	13.1 (5.4)	53	NR	1.0 (-2.0, 5.5)***	14.2 (6.6)	39	NR	0.0 (-2.0, 3.0)***	NS
Meewsen, 2012[393] Good	Caregiver + patient	Anx (STAI-State, 20-80, ↓)	IG1	6	34.9 (9.7)	80	NR	NR	36.5 (9.3)	78	NR	NR	Adj MD (95% CI)=3.55 (1.29, 5.81), 0.002
	Caregiver + patient	Anx (STAI-State, 20-80, ↓)	IG1	12	34.9 (9.7)	78	NR	NR	36.5 (9.3)	75	NR	NR	Adj MD (95% CI)=2.35 (0.35, 4.36), 0.02
	Caregiver + patient	Anx (STAI-Trait, 20-80, ↓)	IG1	12	34.0 (10.2)	80	NR	NR	34.6 (9.1)	78	NR	NR	Adj MD (95% CI)=2.14 (0.24, 4.03), 0.03
	Caregiver + patient	Dep (CES-D, 0-60, ↓)	IG1	6	9.3 (7.6)	80	NR	NR	9.8 (7.6)	78	NR	NR	Adj MD (95% CI)=0.05 (-2.04, 2.13), 0.96
	Caregiver + patient	Dep (CES-D, 0-60, ↓)	IG1	12	9.3 (7.6)	78	NR	NR	9.8 (7.6)	75	NR	NR	Adj MD (95% CI)=2.09 (0.15, 4.02), 0.04
Samus, 2014*[395] Fair	Caregiver + patient	Dep (GDS-15, 0-15, ↓)	IG1	18	2.85 (3.1)‡	106	2.93 (0.34)‡	NR	2.54 (0.23)‡	183	3.01 (0.28)‡	NR	MDC (95% CI)=-0.38 (-1.0, 0.25), 0.43
Other Interventions													
Charlesworth, 2008[399] Fair	Caregiver	Anx (HADS-A, 0-21, ↓)	IG1	6	7.55 (4.58)	104	6.35 (4.46)	NR	7.97 (4.68)	113	6.96 (4.37)	NR	LSM change (95% CI)=0.22 (-0.43, 0.97),

Appendix H Table 2. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Mental Health Outcomes, by Intervention Type

Author, year Quality	Audience	Symptom (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Caregiver	Anx (HADS-A, 0-21, ↓)	IG1	15	7.55 (4.58)	96	6.55 (4.54)	NR	7.97 (4.68)	106	7.55 (4.47)	NR	LSM change (95% CI)=0.61 (-0.33, 1.55),
	Caregiver	Anx (HADS-A, 0-21, ↓)	IG1	22	7.55 (4.58)	93	6.55 (4.49)	NR	7.97 (4.68)	97	6.97 (4.50)	NR	LSM change (95% CI)=-0.04 (-1.10, 1.03),
Charlesworth, 2008[399] Fair	Caregiver	Dep (HADS-D, 0-21, ↓)	IG1	6	6.73 (3.63)	104	6.03 (3.63)	NR	6.96 (3.94)	113	5.84 (3.96)	NR	LSM change (95% CI)=-0.48 (-1.23, 0.26), 0.20
	Caregiver	Dep (HADS-D, 0-21, ↓)	IG1	15	6.73 (3.63)	96	6.03 (4.00)	NR	6.96 (3.94)	106	6.71 (4.18)	NR	LSM change (95% CI)=0.47 (-0.50, 1.44), 0.34
	Caregiver	Dep (HADS-D, 0-21, ↓)	IG1	22	6.73 (3.63)	93	6.25 (4.12)	NR	6.96 (3.94)	97	6.35 (4.59)	NR	LSM change (95% CI)=-0.21 (-1.32, 0.90), 0.71
Connell, 2009[400] Fair	Caregiver	Dep (CES-D, 0-20, ↓)	IG1	6	9.4 (2.9)	74	8.1 (3.0)	NR	7.9 (2.8)	63	8.3 (2.9)	NR	NS
	Caregiver	Dep (CES-D, 0-20, ↓)	IG1	13	9.4 (2.9)	69	8.5 (2.8)	NR	7.9 (2.8)	61	7.7 (2.7)	NR	NS
	Caregiver	Perc Stress (Cohen PSS, 0-4, ↓)	IG1	6	1.9 (0.5)	74	1.7 (0.6)	NR	1.8 (0.5)	63	1.8 (0.6)	NR	NR, <0.05
	Caregiver	Perc Stress (Cohen PSS, 0-4, ↓)	IG1	12	1.9 (0.5)	69	1.8 (0.6)	NR	1.8 (0.5)	61	1.7 (0.6)	NR	NS
King, 2002[403] Fair	Caregiver	Anx (TMAS, 0-20, ↓)	IG1	12	6.4 (4.3)	45	6.3 (4.3)	NR	8.9 (4.5)	40	7.2 (4.9)	NR	NS
	Caregiver	Dep (BDI, 0-63, ↓)	IG1	12	10.7 (6.5)	45	7.4 (4.8)	NR	13.7 (6.3)	40	9.4 (7.2)	NR	NS
	Caregiver	Perc Stress (Cohen PSS, 0-56, ↓)	IG1	12	28.1 (8.3)	45	24.8 (8.1)	NR	29.3 (6.8)	40	26.6 (8.5)	NR	NR
Logiudice, 1999[405] Fair	Caregiver + patient	Psych Health (GHQ-30, 0-90, ↓)	IG1	6	6.8 (7.2)	23	NR	0.79 (NR)	8.3 (7.4)	16	NR	-0.14 (NR)	NR, 0.50
	Caregiver + patient	Psych Health (GHQ-30, 0-90, ↓)	IG1	12	6.8 (7.2)	17	NR	2.50 (NR)	8.3 (7.4)	15	NR	2.23 (NR)	NR, 0.90
Prick, 2015*[408] Fair	Caregiver + patient	Dep (CES-D, 0-60, ↓)	IG1	3	10.84 (6.85)	57	13.71 (8.18)	NR	11.02 (8.57)	54	10.94 (8.42)	NR	logBeta (95% CI)=0.14 (-0.04, 0.33), 0.13
	Caregiver + patient	Dep (CES-D, 0-60, ↓)	IG1	6	10.84 (6.85)	57	13.62 (7.18)	NR	11.02 (8.57)	54	11.38 (8.56)	NR	logBeta (95% CI)=0.07 (-

Appendix H Table 2. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Mental Health Outcomes, by Intervention Type

Author, year Quality	Audience	Symptom (Instrument, range, direction)	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
													0.10, 0.25), 0.41
Winter, 2006[411] Fair	Caregiver	Dep (CES-D, 0-60, ↓)	IG1	6	15.9 (11.1)	53	18.7 (7.19)	NR	14.1 (10.8)	49	20.2 (7.20)	NR	NR, 0.121

* New study
† N (%) of participants scoring ≥15 on CES-D, indicating extremely high levels of depression symptoms
‡ Standard error
§ N (%) of participants scoring ≥8 on CES-D, indicating clinically significant depression symptoms
‖ Number (%) of participants scoring ≥8 on HADS-A (clinically significant anxiety)
¶ N (%) of participants scoring ≥16 on CES-D, indicating clinically significant depression symptoms
# Odds of scoring ≥15 on CES-D, indicating extremely high levels of depression symptoms
** Number (%) of participants scoring ≥9 on HADS-A indicating clinically significant anxiety symptoms
†† N (%) of participants scoring ≥9 on HADS-D, indicating clinically significant depression symptoms
‡‡ N (%) of participants scoring ≥11 on GDS, indicating clinically significant depression symptoms
§§ Odds of scoring ≥10 on BDI, indicating clinically significant depression symptoms
‖‖ N (%) of participants scoring <11.35 on BDI, indicating absence of clinically significant depression symptoms
¶¶ 95% CI
Least squares mean
*** Median change (IQR)

Abbreviations: AD = Alzheimer's Disease; Adj MD = adjusted mean difference; Anx = anxiety; BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory – Second Edition; BL = baseline; BSI-A = Brief Symptom Inventory, Anxiety subscale; BSI-D = Brief Symptom Inventory, depression subscale; CES-D = Center for Epidemiologic Studies – Depression; CES-D-10 = 10-item Center for Epidemiologic Studies – Depression; CG = control group; CI = confidence interval; Cohen PSS = Cohen Perceived Stress Scale; D = dichotomized; Dep = depression; ES = effect size; FU = followup; GDS = Geriatric Depression Scale; GDS-15 = Geriatric Depression Scale-15 item; GHQ-12 = General Health Questionnaire-12 item; GHQ-28 = General Health Questionnaire-28 item; GHQ-30 = General Health Questionnaire-30 item; HADS-A = Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D = Hospital Anxiety and Depression Scale, Depression subscale; HADS-T = Hospital Anxiety and Depression Scale, Total score; HDRS = Hamilton Depression Rating Scale; HR = hazard ratio; HSQ-12 = Health Status Questionnaire, mental health domain; IG = intervention group; Int arm = intervention arm; IRR = incident rate ratio; LSM = least squares mean; MAACL = Multiple Affect Adjective Checklist; MADRS = Montgomery Asberg Depression Rating Scale; MCI = mild cognitive impairment; MD = mean difference; mo. = months; NA = not applicable; NAS = Negative Affect Scale; NR = not reported; NS = not statistically significant; OR = odds ratio; Perc Stress = perceived stress; PHQ-4 = Patient Health Questionnaire-4 items; PHQ-9 = Patient Health Questionnaire-9 items; RSS = Relative Stress Scale; SD = standard deviation; SE = standard error; STAI = State-Trait Anxiety Inventory; STPI = State-Trait Personality Inventory; TMAS = Taylor Manifest Anxiety Scale-Short form

Appendix H Table 3. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Quality of Life Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Psychoeducation Interventions													
Barnes, 2018*[325] Fair	Caregiver	ACQOL (0-120)	IG1	3	69.6 (NR)	27	73.9 (NR)	4.3 (NR)	69.4 (NR)	25	69.2 (NR)	-0.2 (NR)	NR, 0.138
Berwig, 2017*[327] Fair	Caregiver	SF-12 MCS (0-100)	IG1	6	43.7 (11.1)	41	NR	2.398 (8.703)	49.0 (10.6)	40	NR	-2.528 (8.556)	ES=0.571, 0.012
	Caregiver	SF-12 MCS (0-100)	IG1	9	43.7 (11.1)	31	NR	3.868 (10.662)	49.0 (10.6)	31	NR	-4.618 (8.157)	ES=0.902, 0.001
	Caregiver	SF-12 PCS (0-100)	IG1	6	43.6 (10.7)	41	NR	2.600 (9.960)	44.1 (10.7)	40	NR	-1.310 (7.711)	ES=0.443, 0.052
	Caregiver	SF-12 PCS (0-100)	IG1	9	43.6 (10.7)	31	NR	-0.053 (9.591)	44.1 (10.7)	31	NR	0.191 (6.699)	ES=0.030, 0.908
Duggleby, 2018*[337] Fair	Caregiver	SF-12 MCS (0-100)	IG1	3	NR	101	NR	NR	NR	98	NR	NR	LSM (95% CI)=-0.23 (-3.25, 2.80), 0.88
	Caregiver	SF-12 MCS (0-100)	IG1	6	NR	101	NR	NR	NR	98	NR	NR	Beta (95% CI)=0.68 (-0.76, 2.12), 0.35
	Caregiver	SF-12 PCS (0-100)	IG1	3	NR	101	NR	NR	NR	98	NR	NR	LSM (95% CI)=-0.02 (-2.07, 2.01), 0.98
	Caregiver	SF-12 PCS (0-100)	IG1	6	NR	101	NR	NR	NR	98	NR	NR	NS
Fung, 2002*[339] Fair	Caregiver	WHOQoL-BREF (28-140)	IG1	4	96.90 (14.11)	26	113.21 (9.98)	NR	103.75 (0.68)	26	88.19 (9.56)	NR	F statistic=23.145, 0.000
Gaugler, 2013*[344] Fair	Whole family	Cantril Ladder QoL (0-100)	IG1	4	74.63 (16.71)	54	82.29 (NR)	NR	76.77 (10.62)	53	81.49 (NR)	NR	NR
	Whole family	Cantril Ladder QoL (0-100)	IG1	8	74.63 (16.71)	54	80.56 (NR)	NR	76.77 (10.62)	53	81.12 (NR)	NR	NR
	Whole family	Cantril Ladder QoL (0-100)	IG1	12	74.63 (16.71)	54	80.14 (NR)	NR	76.77 (10.62)	53	80.60 (NR)	NR	NR
	Whole family	Cantril Ladder QoL (0-100)	IG1	18	74.63 (16.71)	54	81.07 (NR)	NR	76.77 (10.62)	53	79.62 (NR)	NR	NR
	Whole family	Cantril Ladder QoL (0-100)	IG1	24	74.63 (16.71)	54	82.63 (NR)	NR	76.77 (10.62)	53	78.41 (NR)	NR	NR

Appendix H Table 3. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Quality of Life Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Whole family	Cantril Ladder QoL (0-100)	IG1	30	74.63 (16.71)	54	83.46 (NR)	NR	76.77 (10.62)	53	77.01 (NR)	NR	NR
	Whole family	Cantril Ladder QoL (0-100)	IG1	36	74.63 (16.71)	54	82.19 (NR)	NR	76.77 (10.62)	53	75.53 (NR)	NR	Beta (SE)=-0.21 (1.59), NS
Graff, 2006[349] Fair	Caregiver + patient	DQOL single item (1-5)	IG1	3	3.3 (0.9)	67	4.1 (0.6)	NR	3.4 (0.8)	65	3.4 (0.8)	NR	Adj MD (95% CI)=0.9 (0.6, 1.1), <0.0001
Judge, 2013*[353] Fair	Caregiver + patient	QOL-AD (0-18)	IG1	3	10.88 (2.73)	59	10.92 (3.04)	NR	10.92 (3.76)	59	10.69 (3.40)	NR	Beta=0.04,>0.05
Kurz, 2010[355] Fair	Caregiver	SF-36 emotional well-being (0-100)	IG1	15	NR	127	NR	-5.3 (24.5)	NR	113	NR	-7.8 (25.9)	NR, 0.33
	Caregiver	SF-36 role functioning, emotional (0-100)	IG1	15	NR	125	NR	5.3 (48.5)	NR	115	NR	-10.4 (51.2)	NR, 0.01
	Caregiver	SF-36 social functioning (0-100)	IG1	15	NR	127	NR	2.3 (31.3)	NR	115	NR	2.0 (33.5)	NR, 0.64
Laakkonen, 2016*[357] Fair	Caregiver + patient	SF-36 MCS (0-100)	IG1	3	51.0 (9.1)	67	NR	-0.22 (NR)	47.6 (45.1)	67	NR	-0.25 (NR)	NR, 0.99
	Caregiver + patient	SF-36 MCS (0-100)	IG1	9	51.0 (9.1)	67	NR	-1.21 (NR)	47.6 (45.1)	67	NR	-0.42 (NR)	NR, 0.58
	Caregiver + patient	SF-36 PCS (0-100)	IG1	3	44.0 (9.8)	67	NR	1.0 (NR)	43.8 (10.5)	67	NR	-2.0 (NR)	Cohen's D=0.38,0.006
	Caregiver + patient	SF-36 PCS (0-100)	IG1	9	44.0 (9.8)	67	NR	-0.0 (NR)	43.8 (10.5)	67	NR	-1.7 (NR)	NR, 0.13
Martin-Carrasco, 2009[362] Fair	Caregiver	SF-36 emotional well-being (0-100)	IG1	10	60.2 (9.5)	44	63.0 (9.2)	NR	60.8 (8.1)	38	60.9 (8.3)	NR	NR, 0.3197
	Caregiver	SF-36 energy/vitality (0-100)	IG1	10	47.4 (21.6)	44	53.8 (15.9)	NR	42.8 (16.1)	38	38.9 (17.9)	NR	NR, 0.0002
	Caregiver	SF-36 general health (0-100)	IG1	10	48.4 (18.5)	44	53.4 (18.0)	NR	44.6 (19.2)	38	40.1 (15.7)	NR	NR, 0.0011
	Caregiver	SF-36 pain (0-100)	IG1	10	63.0 (25.9)	44	74.0 (18.7)	NR	61.4 (26.2)	38	61.7 (26.9)	NR	NR, 0.0157
	Caregiver	SF-36 physical functioning (0-100)	IG1	10	74.3 (25.5)	44	80.1 (20.7)	NR	71.7 (21.4)	55	68.8 (25.6)	NR	NR, 0.0310
	Caregiver	SF-36 role functioning, emotional (0-100)	IG1	10	57.6 (45.7)	44	73.5 (41.0)	NR	63.2 (39.4)	38	47.4 (48.2)	NR	NR, 0.0160

Appendix H Table 3. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Quality of Life Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Caregiver	SF-36 role functioning, physical (0-100)	IG1	10	61.4 (44.6)	44	84.7 (34.6)	NR	53.9 (44.5)	38	56.8 (47.0)	NR	NR, 0.0074
	Caregiver	SF-36 social functioning (0-100)	IG1	10	63.4 (28.5)	44	71.0 (23.4)	NR	70.8 (27.0)	38	58.9 (27.7)	NR	NR, 0.0488
Martin-Carrasco, 2014*[361] Fair	Caregiver	SF-12 emotional well-being (0-100)	IG1	4	60.5 (22.9)	115	NR	1.53 (23.8)	60.0 (23.9)	123	NR	2.76 (19.2)	MDC (95% CI)=-1.23 (-7.22, 4.75), NS
	Caregiver	SF-12 energy/vitality (0-100)	IG1	4	53.3 (28.6)	115	NR	2.04 (28.6)	59.5 (30.7)	123	NR	-1.67 (29.5)	MDC (95% CI)=3.71 (-4.34, 11.76), NS
	Caregiver	SF-12 general health (0-100)	IG1	4	40.9 (21.5)	115	NR	-3.12 (19.3)	41.0 (21.3)	123	NR	1.89 (20.0)	MDC (95% CI)=-5.01 (-10.48, 0.45), NS
	Caregiver	SF-12 pain (0-100)	IG1	4	68.4 (32.6)	115	NR	6.38 (25.7)	71.2 (32.0)	123	NR	-0.47 (34.3)	MDC (95% CI)=6.85 (-1.58, 15.28), NS
Martin-Carrasco, 2014*[361] Fair	Caregiver	SF-12 physical functioning (0-100)	IG1	4	72.7 (33.3)	115	NR	-1.02 (30.0)	66.7 (35.2)	123	NR	0.0 (41.3)	MDC (95% CI)=-1.02 (-11.10, 9.06),
	Caregiver	SF-12 role functioning, emotional (0-100)	IG1	4	77.3 (25.3)	115	NR	-3.06 (27.7)	78.4 (24.6)	123	NR	1.19 (24.5)	MDC (95% CI)=-4.25 (-11.48, 2.98), NS
	Caregiver	SF-12 role functioning, physical (0-100)	IG1	4	66.9 (27.0)	115	NR	3.09 (26.9)	72.3 (27.2)	123	NR	1.30 (26.7)	MDC (95% CI)=1.80 (-5.63, 9.22), NS
	Caregiver	SF-12 social functioning (0-100)	IG1	4	73.0 (28.2)	115	NR	-4.08 (31.6)	74.1 (28.0)	123	NR	-3.30 (30.3)	MDC (95% CI)=-0.78 (-9.33, 7.77), NS
Tremont, 2015*[373] Fair	Caregiver	EQ-VAS (0-100)	IG1	6	80.08 (16.07)	133	79.87 (15.00)	NR	77.14 (17.61)	117	77.59 (15.69)	NR	NR, 0.748
Voigt-Radloff, 2011[375] Fair	Caregiver + patient	DQOL single item (1-5)	IG1	6	3.1 (0.8)	51	3.0 (0.7)	NR	3.1 (0.7)	48	3.2 (0.8)	NR	MD (95% CI)=0.2 (-0.1, 0.5), NS
	Caregiver + patient	DQOL single item (1-5)	IG1	12	3.1 (0.8)	51	2.8 (0.8)	NR	3.1 (0.7)	48	3.0 (0.8)	NR	MD (95% CI)=0.2 (-0.1, 0.5), NS
	Caregiver + patient	SF-12 MCS (0-100)	IG1	6	50.9 (9.1)	40	50.2 (9.1)	NR	49.8 (10.7)	38	50.1 (10.7)	NR	MD (95% CI)=0.0 (-4.5, 4.4), NS
	Caregiver + patient	SF-12 MCS (0-100)	IG1	12	50.9 (9.1)	40	49.5 (11.9)	NR	49.8 (10.7)	38	47.7 (10.7)	NR	MD (95% CI)=-1.7 (-6.7, 3.4), NS

Appendix H Table 3. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Quality of Life Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Caregiver + patient	SF-12 PCS (0-100)	IG1	6	42.4 (11.5)	40	45.4 (10.7)	NR	43.5 (11.3)	38	45.0 (10.5)	NR	MD (95% CI)=-0.4 (-5.2, 4.4), NS
	Caregiver + patient	SF-12 PCS (0-100)	IG1	12	42.4 (11.5)	40	42.7 (10.7)	NR	43.5 (11.3)	38	41.6 (11.7)	NR	MD (95% CI)=-1.0 (-6.1, 4.0), NS
Waldorff, 2012[376] Good	Caregiver + patient	EQ-VAS (0-100)	IG1	6	79.3 (16.3)	141	81.6 (16.4)	2.07 (16.3)	81.4 (16.3)	150	80.3 (18.2)	-1.25 (14.3)	MDC (95% CI)=2.61 (0.76, 4.46), 0.006
	Caregiver + patient	EQ-VAS (0-100)	IG1	12	79.3 (16.3)	128	79.5 (16.0)	0.02 (16.3)	81.4 (16.3)	144	81.8 (17.0)	-0.38 (14.5)	MDC (95% CI)=-0.65 (-1.70, 0.39), 0.22
	Caregiver + patient	EQ-VAS (0-100)	IG1	36	79.3 (16.3)	163	80.3 (NR)	0.14 (NR)	81.4 (16.3)	167	79.5 (NR)	-2.71 (NR)	NR, 0.28
Wang, 2011*[377] Fair	Caregiver + patient	WHOQoL-BREF (28-144)	IG1	6	65.9 (13.0)	40	78.8 (19.0)	NR	67.0 (13.5)	40	68.9 (15.7)	NR	NR, <0.001
Wilz, 2018*[380] Good	Caregiver	WHOQoL-BREF (0-100)	IG1	6	50.18 (17.99)	139	55.58 (17.75)	NR	47.48 (17.99)	134	50.00 (18.37)	NR	MD=0.386, 0.006
	Caregiver	WHOQoL-BREF (0-100)	IG1	12	50.18 (17.99)	139	54.20 (19.55)	NR	47.48 (17.99)	134	53.35 (18.91)	NR	MD=0.057, 0.714
Care/Case Management Interventions													
Chien, 2011*[384] Good	Whole family	WHOQoL-BREF (28-144)	IG1	6	64.9 (15.0)	44	75.1 (16.8)	NR	67.1 (15.5)	44	69.8 (16.7)	NR	NR
	Whole family	WHOQoL-BREF (28-144)	IG1	12	64.9 (15.0)	444	81.4 (16.0)	NR	67.1 (15.5)	44	65.2 (17.5)	NR	F statistic=6.7, <0.001
	Caregiver + patient	WHOQoL-BREF (28-144)	IG1	12	64.8 (13.0)	46	80.4 (15.0)	NR	67.1 (15.5)	46	65.2 (17.5)	NR	MD (SE)=15.2 (1.1), 0.01
	Caregiver + patient	WHOQoL-BREF (28-144)	IG1	18	64.8 (13.0)	45	82.7 (13.5)	NR	67.1 (15.5)	45	64.5 (13.1)	NR	MD (SE)=18.2 (1.2), 0.005
Jansen, 2011[390] Fair	Caregiver	SF-36 MCS (0-100)	IG1	6	51.0 (NR)	54	48.7 (NR)	NR	48.0 (NR)	45	49.1 (NR)	NR	NS
	Caregiver	SF-36 MCS (0-100)	IG1	12	51.0 (NR)	54	48.2 (NR)	NR	48.0 (NR)	45	47.7 (NR)	NR	F statistic=1.37, 0.26
	Caregiver	SF-36 PCS (0-100)	IG1	6	44.5 (NR)	54	45.5 (NR)	NR	48.0 (NR)	45	46.5 (NR)	NR	NS
	Caregiver	SF-36 PCS (0-100)	IG1	12	44.5 (NR)	54	46.0 (NR)	NR	48.0 (NR)	45	47.5 (NR)	NR	F statistic=1.06, 0.35
Lam, 2010[391] Fair	Caregiver + patient	PWI-A (0-100)	IG1	4	63.6 (15.1)	57	NR	1.4‡ (NR)	61.2 (18.5)	42	NR	-4.3‡ (NR)	NS

Appendix H Table 3. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Quality of Life Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
	Caregiver + patient	PWI-A (0-100)	IG1	12	63.6 (15.1)	53	NR	2.9‡ (NR)	61.2 (18.5)	39	NR	0.0‡ (NR)	NS
Meewsen, 2012[393] Good	Caregiver + patient	QOL-AD (13-52)	IG1	6	37.6 (3.6)	80	NR	NR	38.5 (4.7)	78	NR	NR	Adj MD (95% CI)=-0.20 (-1.07, 0.66), 0.64
	Caregiver + patient	QOL-AD (13-52)	IG1	12	37.6 (3.6)	78	NR	NR	38.5 (4.7)	75	NR	NR	Adj MD (95% CI)=0.17 (-0.70, 1.04), 0.70
Samus, 2014*[395] Fair	Caregiver + patient	SF-12 MCS (0-100)	IG1	18	48.89 (1.08)§	106	48.45 (1.22)§	NR	48.64 (0.82)§	183	47.54 (1.00)§	NR	MDC (95% CI)=-0.66 (-1.9, 3.2), 0.69
	Caregiver + patient	SF-12 PCS (0-100)	IG1	18	48.88 (1.11)§	106	49.31 (1.25)§	NR	48.11 (0.84)§	183	47.00 (1.02)§	NR	MDC (95% CI)=1.53 (-1.1, 4.2), 0.43
Vickrey, 2006[397] Good	Caregiver	EQ-5D index value (assume 0-1)	IG1	12	0.83 (0.17)	205	0.83 (0.18)	NR	0.80 (0.22)	156	0.79 (0.22)	NR	Adj MD (95% CI)=0.02 (-0.01, 0.06), 0.19
	Caregiver	EQ-5D index value (assume 0-1)	IG1	17	0.83 (0.17)	166	0.81 (0.16)	NR	0.80 (0.22)	124	0.77 (0.23)	NR	Adj MD (95% CI)=0.02 (-0.01, 0.06), 0.13
Xiao, 2016*[398] Fair	Caregiver	SF-36 MCS (0-100)	IG1	6	30.3 (5.3)	31	37.1 (8.2)	NR	27.3 (10.9)	30	24.7 (10.1)	NR	NR
Xiao, 2016*[398] Fair	Caregiver	SF-36 MCS (0-100)	IG1	12	30.3 (5.3)	31	38.7 (7.0)	NR	27.3 (10.9)	30	23.0 (8.6)	NR	F statistic=22.35, <0.001
	Caregiver	SF-36 PCS (0-100)	IG1	6	42.2 (7.2)	31	41.8 (7.6)	NR	44.9 (8.5)	30	41.8 (8.5)	NR	NR
	Caregiver	SF-36 PCS (0-100)	IG1	12	42.2 (7.2)	31	41.1 (7.7)	NR	44.9 (8.5)	30	41.6 (8.7)	NR	F statistic=2.68, 0.08
Other Interventions													
Charlesworth, 2008[399] Fair	Caregiver	EQ-VAS (0-100)	IG1	6	74.0 (16.8)	104	75.7 (17.0)	NR	73.1 (18.1)	113	72.9 (17.7)	NR	LSM (95% CI)=-2.06 (-5.51, 1.38), NR
	Caregiver	EQ-VAS (0-100)	IG1	15	74.0 (16.8)	96	73.8 (18.3)	NR	73.1 (18.1)	106	69.9 (18.1)	NR	LSM (95% CI)=-2.33 (-6.88, 2.23), NR
	Caregiver	EQ-VAS (0-100)	IG1	22	74.0 (16.8)	93	72.5 (19.7)	NR	73.1 (18.1)	97	68.1 (18.2)	NR	LSM (95% CI)=-3.03 (-8.42, 2.35), NR

Appendix H Table 3. Caregiver and Caregiver-Patient Dyad Interventions: Detailed Results for Caregiver Quality of Life Outcomes, by Intervention Type

Author, year Quality	Audience	Instrument (range)†	Int arm	Time, mo.	IG BL mean (SD)	IG n at FU	IG FU mean (SD)	IG mean change (SD) from BL	CG BL mean (SD)	CG n at FU	CG FU mean (SD)	CG mean change (SD) from BL	Between group difference, p-value
Leach, 2015*[404] Good	Caregiver	AQoL-8D Mental superdomain (0-1)	IG1	3	0.35 (0.21)	8	0.42 (0.22)	NR	0.30 (0.11)	9	0.29 (0.07)	NR	Adj MD (SD)=0.09 (0.14), 0.024
	Caregiver	AQoL-8D Mental superdomain (0-1)	IG1	6	0.35 (0.21)	8	0.37 (0.22)	NR	0.30 (0.11)	9	0.33 (0.10)	NR	Adj MD (SD)=0.004 (0.14), 0.359
	Caregiver	AQoL-8D Physical superdomain (0-1)	IG1	3	0.66 (0.24)	8	0.77 (0.23)	NR	0.73 (0.17)	9	0.76 (0.14)	NR	Adj MD (SD)=0.05 (0.27), 0.043
	Caregiver	AQoL-8D Physical superdomain (0-1)	IG1	6	0.66 (0.24)	8	0.74 (0.21)	NR	0.73 (0.17)	9	0.79 (0.14)	NR	Adj MD (SD)=-0.006 (0.22), 0.669
	Caregiver	AQoL-8D utility score (0-1)	IG1	3	0.65 (0.23)	8	0.74 (0.21)	NR	0.66 (0.14)	9	0.67 (0.10)	NR	Adj MD (SD)=0.08 (0.19), 0.878
	Caregiver	AQoL-8D utility score (0-1)	IG1	6	0.65 (0.23)	8	0.70 (0.21)	NR	0.66 (0.14)	9	0.71 (0.12)	NR	Adj MD (SD)=-0.002 (0.17), 0.878

* New study
† Higher values indicate better outcomes for all instruments
‡ Median change
§ Standard error

Abbreviations: ACQOL = Adult Carers Quality of Life scale; Adj MD = adjusted mean difference; AQoL-8D = Assessment of Quality of Life 8-demension; BL = baseline; CG = control group; CI = confidence interval; DQOL = Dementia Quality of Life; EQ-5D = EuroQol 5-Dimensions; EQ-VAS = EuroQol Visual Analog Scale; FU = followup; IG = intervention group; Int arm = intervention arm; MD = mean difference; MDC = mean difference in change; mo. = months; NR = not reported; NS = not statistically significant; PWI-A = Personal Well-being Index-Adults; QOL = Quality of Life; QOL-AD = Quality of Life in Alzheimer's Disease; SD = standard deviation; SE = standard error; SF-12 = Short Form 12-item SF-36 Short Form 36-item; SF-36 MCS = Short Form 36-item, Mental Component Summary; SF-36 PCS = Short Form 36-item, Physical Component Summary; WHOQoL-BREF = World Health Organization Quality of Life Measure-Brief Version