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Screening for Cognitive Impairment in Older Adults: A Systematic Review for the U.S. Preventive Services Task Force

Jennifer S. Lin, MD, MCR; Elizabeth O'Connor, PhD; Rebecca C. Rossom, MD, MCR; Leslie A. Perdue, MPH; and Elizabeth Eckstrom, MD, MPH

Background: Earlier identification of cognitive impairment may reduce patient and caregiver morbidity.

Purpose: To systematically review the diagnostic accuracy of brief cognitive screening instruments and the benefits and harms of pharmacologic and nonpharmacologic interventions for early cognitive impairment.

Data Sources: MEDLINE, PsycINFO, and the Cochrane Central Register of Controlled Trials through December 2012; systematic reviews; clinical trial registries; and experts.

Study Selection: English-language studies of fair to good quality, primary care–feasible screening instruments, and treatments aimed at persons with mild cognitive impairment or mild to moderate dementia.

Data Extraction: Dual quality assessment and abstraction of relevant study details.

Data Synthesis: The Mini-Mental State Examination ($k = 25$) is the most thoroughly studied instrument but is not available for use without cost. Publicly available instruments with adequate test performance to detect dementia include the Clock Drawing Test ($k = 7$), Mini-Cog ($k = 4$), Memory Impairment Screen ($k = 5$), Abbreviated Mental Test ($k = 4$), Short Portable Mental Status Questionnaire ($k = 4$), Free and Cued Selective Reminding Test ($k = 2$), 7-Minute Screen ($k = 2$), and Informant Questionnaire on Cognitive Decline in the Elderly ($k = 5$). Medications approved by the U.S. Food and Drug Administration for Alzheimer disease ($k = 58$) and caregiver interventions ($k = 59$) show a small benefit of uncertain clinical importance for patients and their caregivers. Small benefits are also limited by common adverse effects of acetylcholinesterase inhibitors and limited availability of complex caregiver interventions. Although promising, cognitive stimulation ($k = 6$) and exercise ($k = 10$) have limited evidence to support their use in persons with mild to moderate dementia or mild cognitive impairment.

Limitation: Limited studies in persons with dementia other than Alzheimer disease and sparse reporting of important health outcomes.

Conclusion: Brief instruments to screen for cognitive impairment can adequately detect dementia, but there is no empirical evidence that screening improves decision making. Whether interventions for patients or their caregivers have a clinically significant effect in persons with earlier detected cognitive impairment is still unclear.

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For author affiliations, see end of text.

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Dementia, a decline in cognitive function severe enough to affect social or occupational functioning (1), can be due to Alzheimer disease (AD), vascular dementia, frontotemporal dementia, dementia with Lewy bodies, Parkinson disease with dementia, dementia of mixed cause, or many rarer causes (2). Although the exact prevalence is unknown, researchers estimate that dementia affects between 2.4 million and 5.5 million Americans (2–4). Mild cognitive impairment (MCI) differs from dementia in that it is not severe enough to interfere with independence in daily life (for example, instrumental activities of daily living [IADLs]); however, it may be useful for predicting dementia.

Primary care clinicians may not recognize cognitive impairment when using routine history and physical examination (3, 5) in as many as 76% of patients with dementia or probable dementia (6–8), and most of these patients are not diagnosed until they are at moderate to severe stages of the disease (9). Early identification of cognitive impairment would ideally allow patients and their families to receive care at an earlier stage in the disease process, which could lead to improved prognosis and decreased morbidity. Health, psychological, and social benefits from early recognition of dementia through education and improved decision making may make screening valuable even if early treatment cannot alter the natural history of dementia by preventing or slowing the rate of cognitive decline (10).

In 2003, the U.S. Preventive Services Task Force (USPSTF) concluded that there was insufficient evidence to recommend for or against routine screening for dementia in older adults (I statement) (11). We conducted this systematic review to support the USPSTF in updating its prior recommendation. The current review addresses the benefits, harms, and diagnostic accuracy of brief screening instruments to detect cognitive impairment in community-dwelling older adults and the benefits and harms of the commonly used treatment and management options for older adults with MCI or early dementia and their caregivers.

Methods

Our review included 5 key questions. First, does screening for cognitive impairment in community-dwelling

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older adults in primary care–relevant settings improve decision-making, patient, family or caregiver, or societal outcomes? Second, what is the test performance of screening instruments to detect cognitive impairment in elderly, community-dwelling primary care patients? Third, what are the harms of screening for cognitive impairment? Fourth, do interventions for MCI or mild to moderate dementia in older adults improve decision-making, patient, family or caregiver, or societal outcomes? Fifth, what are the harms of interventions for cognitive impairment?

Detailed methods, including the analytic framework, search strategies, flow diagrams of the search and selection processes, detailed inclusion criteria, quality assessment, excluded studies, and description of data analyses are publicly available in our full evidence report at www.uspreventiveservicestaskforce.org.

Data Sources and Searches

We first searched for systematic reviews published since 2001 by using MEDLINE; the Cochrane Database of Systematic Reviews; the Database of Abstracts of Reviews of Effects; and publications from the Institute of Medicine, the Agency for Healthcare Research and Quality (AHRQ), and the National Institute for Health and Care Excellence. We used the most relevant existing systematic reviews—1 on screening for dementia (3) and 11 on treatment of dementia and MCI (12–22)—to identify primary studies for inclusion and to develop comprehensive search strategies for each question. We searched MEDLINE, PsycINFO, and the Cochrane Central Register of Controlled Trials from the end search dates of existing reviews until 10 December 2012. We supplemented our searches with expert suggestions, reference lists of systematic reviews, and trial registry platforms for ongoing trials.

Study Selection

Two investigators independently reviewed 16 179 abstracts and 1190 articles (**Figure 1**) against the specified inclusion criteria (**Appendix Table 1**, available at www.annals.org). We resolved discrepancies through consensus and consultation with a third investigator. We included fair- to good-quality English-language studies of community-dwelling adults that were most applicable to primary care in the United States. For screening questions, we included studies that evaluated any brief screening instrument that could be delivered by a clinician in primary care in 10 minutes or less or self-administered in 20 minutes or less. Screening instruments could be administered to the patient or an informant. For treatment questions, we included the major pharmacologic and nonpharmacologic interventions intended for use in older adults with MCI or mild to moderate dementia, excluding Parkinson dementia, to approximate persons with "screen-detected" cognitive impairment. We considered any decision-making, patient, or caregiver health outcome. For harms of screening, we considered any study design reporting harms, including psychological harms and those due to labeling or poor adherence to diagnostic follow-up. For harms of treatment, we focused primarily on serious harms that resulted in unexpected medical care, illness, or death for interventions that showed any evidence of benefit.

Data Extraction and Quality Assessment

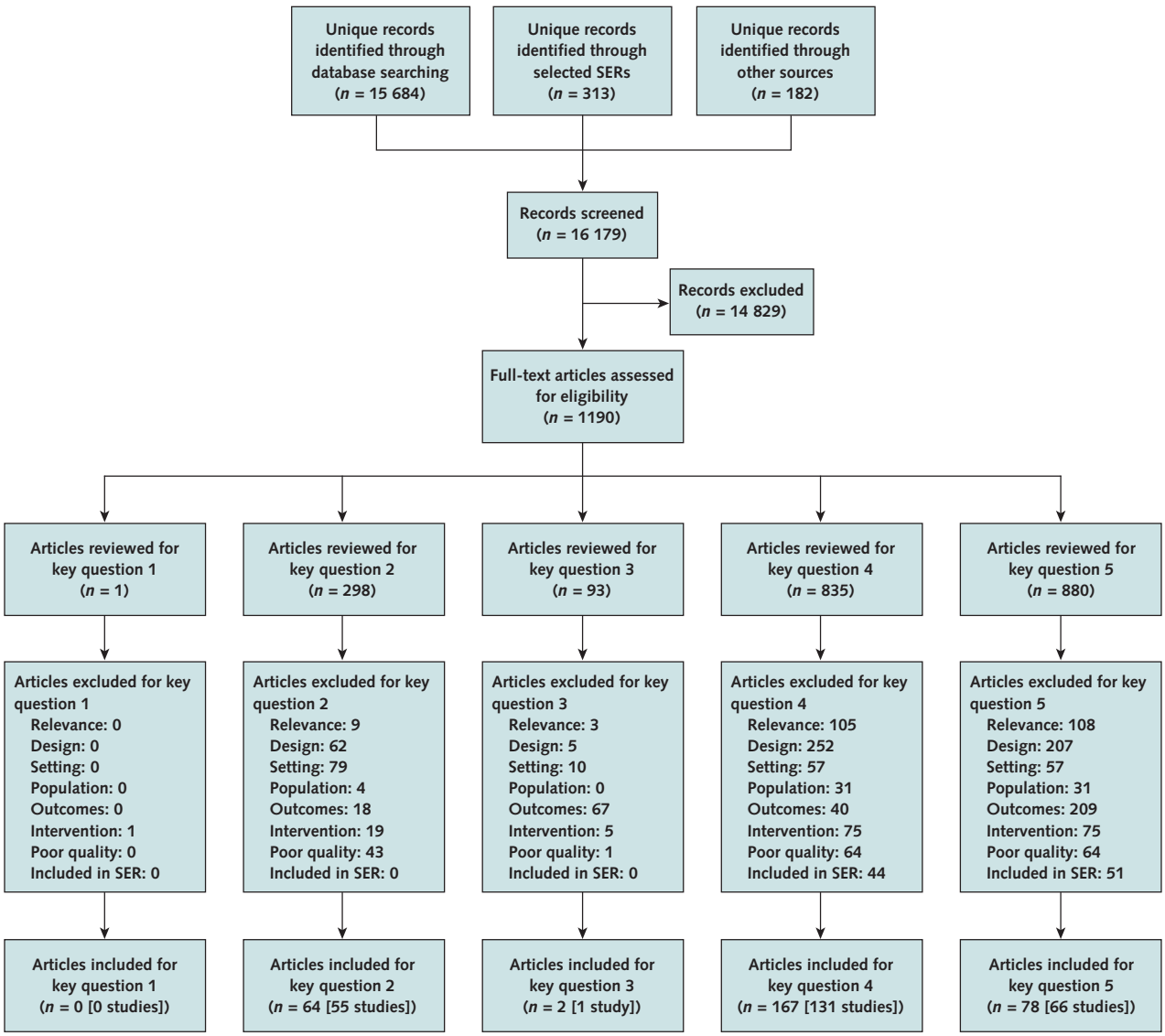
One investigator extracted data, and a second investigator checked the extraction. Two reviewers independently appraised all articles by using the USPSTF's design-specific quality criteria (28). We supplemented these criteria with the National Institute for Health and Care Excellence methodology checklists (29), AMSTAR (A Measurement Tool to Assess Systematic Reviews) for systematic reviews (30), the Newcastle-Ottawa Scale for observational studies (31), and QUADAS (Quality Assessment of Diagnostic Accuracy Studies) for studies of diagnostic accuracy (32). Fair-quality (as opposed to good-quality) studies did not meet at least 1 criterion but had no important limitations that would invalidate the results. The most common limitations in studies excluded because of poor quality were verification bias in diagnostic studies and greater than 40% attrition or inability to assess for criteria due to limited reporting in trials.

Data Synthesis and Analysis

For diagnostic accuracy studies on screening for MCI or dementia, our primary outcomes of interest were sensitivity and specificity at a given cut point for the instrument, by instrument type (according to length of administration) and separated by detection of dementia, MCI, or both. We synthesized and reported the results for the most commonly used cut points, when applicable. We conducted quantitative syntheses of sensitivity and specificity if sufficient data were presented in more than 2 similar studies based on populations, scoring or cut points, and outcomes. We ran a bivariate model using the "metandi" procedure in Stata 11.2 (StataCorp, College Station, Texas), which models sensitivity and specificity simultaneously, thus accounting for the correlation between these variables (33).

For treatment trials, we grouped interventions into 4 broad categories: U.S. Food and Drug Administration (FDA)–approved medications to treat AD, other medications or dietary supplements, nonpharmacologic interventions for caregiver–patient dyads, and nonpharmacologic interventions meant primarily for the patient. We synthesized results within each category and examined results and the association of key study characteristics with results and effect sizes on commonly reported outcomes. Characteristics included age, sex, severity of cognitive impairment of the patient, caregiver hours, setting, country, intervention components, dosing frequency or intensity, length of follow-up, and study quality. Commonly reported outcomes included measures of cognition, global functioning, and physical functioning. For assessment of global cognitive function, the most commonly used measures in our included studies were the Alzheimer's Disease Assessment

Figure 1. **Summary of evidence search and selection.**



SER = systematic evidence review.

Scale-Cognitive Subscale (ADAS-cog) (34) and the Mini-Mental State Examination (MMSE). Assessment of global function was not commonly reported except in trials evaluating FDA-approved medications for AD, which used the Clinician Interview-Based Impression of Change Plus Caregiver Input (CIBIC-plus) (35). Global physical functioning was measured by various instruments that captured the patient's ability to complete basic ADLs (36) or IADLs (37). The most commonly reported caregiver outcomes were caregiver burden, usually measured with the Zarit Caregiver Burden Interview (38), and caregiver depression, usually measured with the Center for Epidemiologic Studies Depression Scale (39).

We conducted quantitative analyses on important patient outcomes reported in most trials. We analyzed a standardized effect size (Hedge g) based on the differences in change between groups from baseline to follow-up using standard formulas (40–42). For global cognitive measures, a change of 4 points or more on the ADAS-cog over 6 months was considered a clinically important improvement in mild to moderate dementia (43). For standardized effect sizes, standardized mean differences of 0.2 to less than 0.5 were considered small, those 0.5 to less than 0.8 were considered medium, and those 0.8 or greater were considered large (44). We used meta-regressions and visual inspection of forest plots to explore heterogeneity of effect sizes. We assessed the presence of statistical heterogeneity among the studies by using standard chi-square tests and estimated the magnitude of heterogeneity using the I^2 statistic (45). Publication bias was assessed using tests to examine for bias

due to small-study effects (46, 47). We used Stata 11.2 for all statistical analyses.

Role of the Funding Source

The study was funded by AHRQ under a contract to support the work of the USPSTF. Members of the USPSTF and the AHRQ medical officer assisted in the development of the scope of this review.

RESULTS

We found no trials that directly assessed whether screening for cognitive impairment in primary care could affect decision-making, patient or caregiver, or societal outcomes (key question 1) (**Figure 1**). No studies directly addressed the adverse psychological effects of screening or adverse effects from false-positive or false-negative test results (key question 3). We found only 1 fair-quality study showing that approximately half of older adults with positive screening test results for cognitive impairment declined to complete a formal diagnostic work-up for dementia (48, 49). Included evidence, therefore, focused on the diagnostic accuracy of screening instruments (key question 2) and the benefits and harms of different treatment and management options in older adults with early cognitive impairment (key questions 4 and 5). Detailed results are publicly available in our full evidence report at www.uspreventiveservicestaskforce.org.

Test Performance of Brief Cognitive Screening Instruments (Key Question 2)

We identified 55 fair- to good-quality diagnostic accuracy studies of brief screening instruments (29 administered in ≤5 minutes, 19 administered in 6 to 10 minutes, and 5 self-administered) conducted in primary care–relevant populations (**Table 1** of the **Supplement**, available at www.annals.org) (50–88). Forty-six studies provided the test performance for detection of dementia. These studies covered a broad range of older adults selected from the community or primary care practices. Almost all studies had a majority of female participants, but the studies varied in mean age (range, 69 to 95 years) and prevalence of dementia (range, 1.2% to 47.1%). Among trials that reported education level, included adults usually had at least some high school education.

Only 12 brief instruments have been studied more than once in well-designed diagnostic accuracy studies that evaluated their ability to detect dementia in primary care–relevant populations: the MMSE ($k = 25$; $n = 12\,348$), the Clock Drawing Test (CDT) ($k = 7$; $n = 2509$), verbal or category fluency tests ($k = 6$; $n = 2083$), the short or full Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) ($k = 5$; $n = 1251$), the Memory Impairment Screen (MIS) (MIS: $k = 4$; $n = 1671$; MIS by telephone: $k = 1$; $n = 300$), Mini-Cog ($k = 4$; $n = 1570$), the Abbreviated Mental Test (AMT) ($k = 4$; $n = 824$), the Short Portable Mental Status Questionnaire (SPMSQ) ($k = 4$; $n = 1057$), the Mental Status Questionnaire ($k = 2$; $n = 522$), the Free and Cued Selective Reminding Test (FCSRT) ($k = 2$; $n = 734$), the 7-Minute Screen (7MS) ($k = 2$; $n = 553$), and the Telephone Interview for Cognitive Status (TICS) ($k = 2$; $n = 677$) (**Appendix Table 2**, available at www.annals.org). Only 4 studies were of good quality; the rest were of fair quality and had various risks of bias, the most common being partial verification, unclear independence of application or interpretation of screening test and reference standard, selection bias with stratified sampling or sampling of volunteers only, and unclear spectrum of patients due to poor reporting of how study population was derived or percentage of or reasons for attrition. The most common reference standards were criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III), the DSM-IV, or the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association, and formal diagnosis was based on a combination of history, examination, neuropsychological testing, and expert consensus.

The best-studied instrument was the MMSE. Pooled estimates across 14 studies ($n = 10\,185$) resulted in sensitivity of 88.3% (95% CI, 81.3% to 92.9%) and specificity of 86.2% (CI, 81.8% to 89.7%) for the most commonly reported cut points of 23/24 or 24/25. The CDT, Mini-Cog, MIS, SPMSQ, AMT, FCSRT, 7MS, TICS, and IQCODE can also have acceptable test performance; however, less evidence supported the use of each of these instruments and had limited reproducibility in primary care–relevant populations and unknown optimum cut points for each instrument. The CDT had a wider range of sensitivity and specificity (67% to 97.9% and 69% to 94.2%, respectively), and the optimum cut point is unclear from the body of literature we examined. The Mini-Cog probably has better sensitivity than the CDT alone (76% to 100%) but with a possible tradeoff of lower specificity (54% to 85.2%). Although the MIS can have relatively good test performance in screening for dementia (sensitivity, 43% to 86%; specificity, 93% to 97%), the sensitivities in the 2 good-quality studies ($n = 948$) were low (about 40%). Likewise, the AMT can have relatively good test performance in screening for dementia (sensitivity, 42% to 100%; specificity, 83% to 95.4%), but 1 fair-quality study ($n = 289$) had low sensitivity (42%) and no studies were done in the United States. The SPMSQ, FCSRT, 7MS, and TICS also have reasonable test performance, but this is based on a limited number of studies. The verbal fluency tests had worse performance than other instruments regardless of cut point. The IQCODE, a self-administered informant-based screening tool, had a sensitivity of 75% to 87.6% and a specificity of 65% to 91.1%. The 6-Item Screener, Visual Association Test, General Practitioner Assessment of Cognition, ADL/IADL, Benton Orientation Test, Delayed Recall Test, and Short Concord Informant Dementia Scale all had greater than 80% sensitivity and

specificity to detect dementia in a single study, but their test performance has not been reproduced in other primary care–relevant populations.

We found 27 studies designed to assess the diagnostic accuracy of 22 screening instruments to detect MCI in primary care–relevant populations (56–58, 67–69, 73, 74, 78, 83, 86–101). Only 6 instruments were examined in more than 1 study: the MMSE ($k = 15$; $n = 5758$), IQCODE ($k = 4$; $n = 975$), CDT ($k = 4$; $n = 4191$), Mini-Cog ($k = 3$; $n = 1092$), TICS ($k = 3$; $n = 568$), and Montreal Cognitive Assessment ($k = 2$; $n = 251$). Overall, the sensitivity to detect MCI for each of these instruments, except for the IQCODE, was lower than that to detect dementia (data not shown). Results for screening instruments to detect MCI are available in our full evidence report.

Benefits and Harms of Treatment in Early Cognitive Impairment (Key Questions 4 and 5)

We identified 1 systematic review from 2008 and 118 trials that addressed the benefit of the treatment or management of mild to moderate dementia, MCI, or both (**Appendix Table 3**, available at www.annals.org).

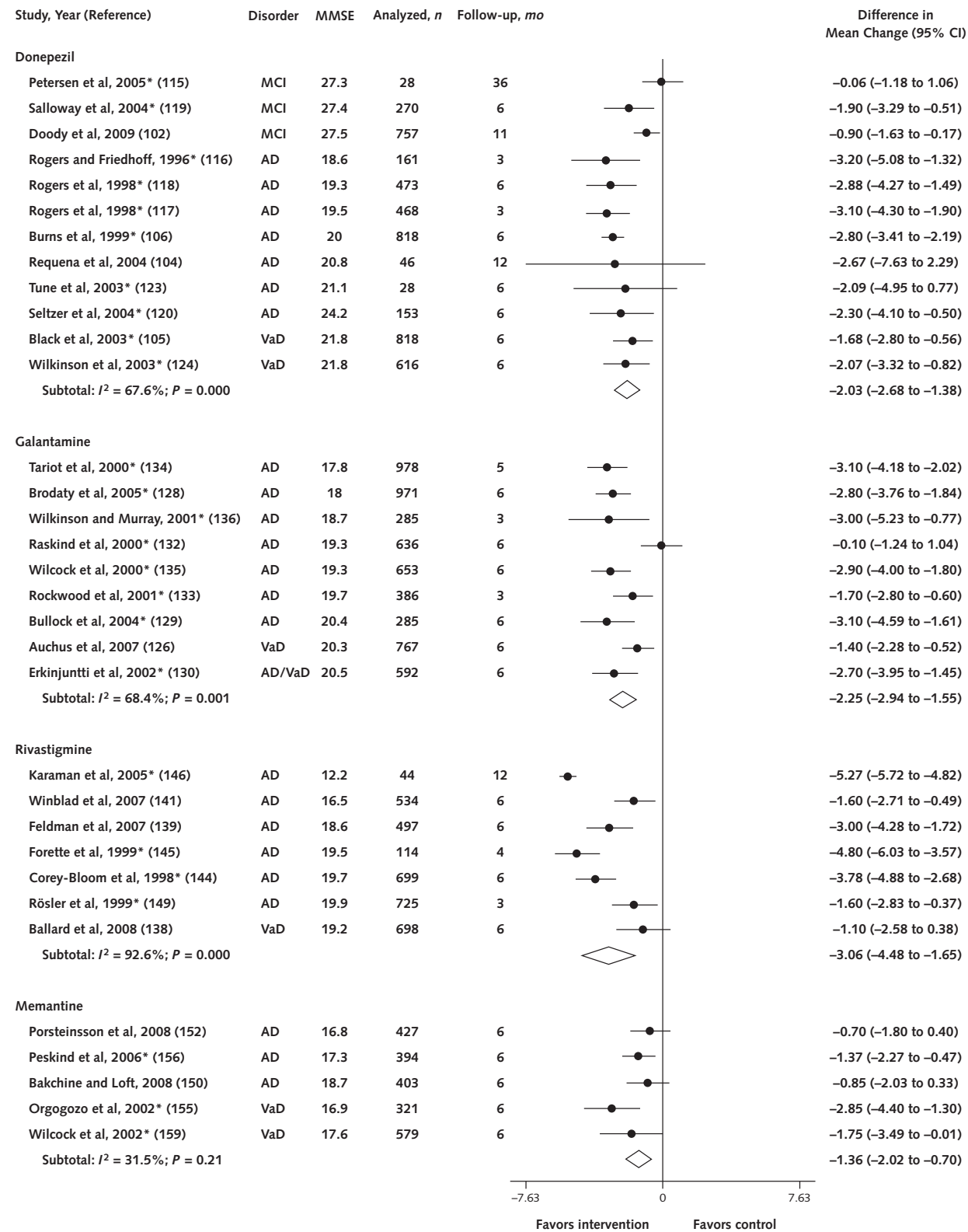
To evaluate adverse effects of treatments with evidence of benefit, we examined the systematic review, 40 trials, and 6 open-label extensions of medication trials that reported harms and 13 observational trials designed to assess medication harms. Most trials (90%) were of fair quality. Common limitations included differences in baseline characteristics, high attrition (>20%), evidence of attrition bias, nonblinded assessment of outcomes, completers-only analyses, and limited reporting to evaluate trial conduct. Medication trials were either exclusively or partially industry-funded.

Pharmacologic Interventions

One well-conducted systematic review of FDA-approved medications for the treatment of AD included 39 randomized, controlled trials of acetylcholinesterase inhibitors (AChEIs) in persons with MCI or mild to moderate dementia (14). We identified an additional 9 randomized, controlled trials published since this systematic review. Overall, on the basis of 48 fair- to good-quality trials ($n = 18\,390$) (donepezil: $k = 24$; $n = 7552$; galantamine: $k = 12$; $n = 6008$; rivastigmine: $k = 12$; $n = 4829$), AChEIs can improve cognitive function and global functioning in the short term (**Appendix Table 3** and **Table 2** of the **Supplement**) (102–149). However, the pooled magnitude of these changes is small, with a change of approximately 1 to 3 points on the ADAS-cog (**Figure 2**). The pooled estimate of benefit for rivastigmine is not reliable given the large statistical heterogeneity. Most available evidence comes from trials in persons with moderate AD with 6 months of follow-up. The average effect of these changes may not be clinically meaningful as defined using commonly accepted values. Only 4 trials ($n = 1960$) were conducted in persons with MCI (102, 115, 119, 131). Measures of global functioning were reported in 30 trials (donepezil, $k = 14$; galantamine, $k = 7$; rivastigmine, $k = 9$). Acetylcholinesterase inhibitors seem to consistently slow the rate of decline of global functioning by a fraction of a point in persons with AD in the short term, as measured by the CIBIC-plus. Only 1 galantamine trial reporting global functioning was conducted in persons with MCI (131). Outcome measures of global physical function were reported in only half of the trials and showed mixed results. Therefore, whether AChEIs can improve physical functioning is unclear given the inconsistent and sparsely reported findings. Six included trials and 7 open-label extension studies of included trials examined outcomes beyond 6 months. These studies generally found persistent statistically significant benefits of unknown clinical importance for commonly reported outcomes, consistent with the 6-month trial outcomes. Two trials evaluating donepezil in persons with MCI did not show any differences in conversion to AD at about 3 years. Withdrawal or discontinuation is more common with AChEIs than with placebo (**Figure 3**) (102, 103, 105–107, 109, 111, 112, 114, 116–130, 132–136, 138–142, 144–147, 149–159, 273–287). Discontinuation rates were 14% for donepezil and rivastigmine and 17% for galantamine. However, total serious adverse events did not seem to differ for these medications across trials with limited duration of follow-up (data not shown). Three small trials reporting zero adverse events are not reflected in these estimates (111, 112, 123). Estimates of total serious adverse events were higher in observational studies than in randomized trials. The definitions of serious adverse events were not commonly described in the included studies. Observational studies suggest that bradycardia and adverse events related to it (for example, fall or syncope) were increased with AChEIs (**Table 3** of the **Supplement**). Memantine is currently FDA-approved for use in moderate to severe AD but has also been evaluated in persons with mild to moderate dementia or MCI. On the basis of 10 fair- to good-quality trials ($n = 3015$), memantine had a benefit similar to that seen with AChEIs on global cognitive functioning in persons with moderate dementia: a change of approximately 1 to 2 points on the ADAS-cog at 6 months (**Appendix Table 3**, **Figure 2**, and **Table 2** of the **Supplement**) (150–159). Only 1 trial had longer-term follow-up, and it showed no differences in cognitive functioning between the memantine and placebo groups at 52 weeks. The effect of memantine on global functioning and physical functioning was inconsistent. Only 1 trial was done in persons with MCI, and it did not report outcome measures of global cognitive or physical function. From trial data, the percentage of persons stopping memantine therapy due to adverse effects was similar to that of placebo (**Figure 3**).

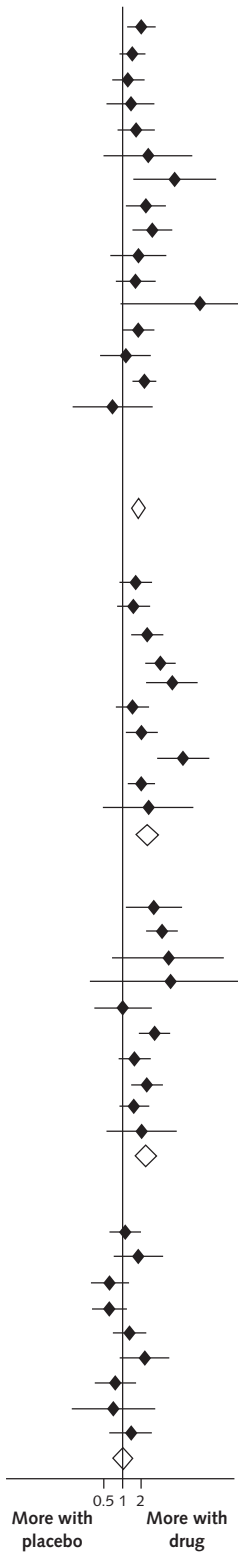
Twenty-six fair- to good-quality trials ($n = 5325$) evaluated other medications or dietary supplements (160–185), including low-dose aspirin ($k = 2$; $n = 459$),

Figure 2. **Meta-analyses of effects of AChEIs and memantine on global cognitive function, measured by the ADAS-cog.**



Weights are from random-effects analysis. AChEI = acetylcholinesterase inhibitor; AD = Alzheimer disease; ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; VaD = vascular dementia.
* Included in the systematic review by Raina and colleagues, 2008 (14).

Figure 3. **Meta-analyses of effects of AChEIs and memantine on withdrawals due to adverse events.**



Study, Year (Reference)	RR (95% CI)	Events, *n/N*	
		Treatment	Control
Donepezil			
Black et al, 2003* (105)	1.98 (1.23–3.17)	45/206	22/199
Burns et al, 1999* (106)	1.42 (0.94–2.15)	76/544	27/274
Courtney et al, 2004* (107)	1.22 (0.72–2.07)	28/282	23/283
Feldman et al, 2001* (109)	1.35 (0.59–3.11)	12/144	9/146
Mohs et al, 2001* (114)	1.62 (0.88–3.01)	24/214	15/217
Rogers and Friedhoff, 1996* (116)	2.56 (0.53–12.44)	5/39	2/40
Rogers et al, 1998* (117)	6.78 (1.57–29.33)	14/158	2/153
Rogers et al, 1998* (118)	2.35 (1.19–4.60)	25/157	11/162
Salloway et al, 2004* (119)	2.99 (1.52–5.88)	29/133	10/137
Seltzer et al, 2004* (120)	1.78 (0.68–4.64)	15/96	5/57
Tariot et al, 2001* (121)	1.61 (0.83–3.15)	19/103	12/105
Thomas et al, 2001* (122)	17.57 (0.99–311.15)	4/20	0/40
Wilkinson et al, 2003* (124)	1.80 (1.04–3.11)	34/215	17/193
Winblad et al, 2001* (125)	1.13 (0.47–2.69)	10/142	9/144
Doody et al, 2009 (102)	2.23 (1.50–3.30)	72/391	32/387
Mori et al, 2012 (103)	0.69 (0.17–2.86)	3/37	4/34
Kemp et al, 2003* (111)	Excluded	0/6	0/6
Krishnan et al, 2003* (112)	Excluded	0/34	0/33
Tune et al, 2003* (123)	Excluded	0/14	0/14
Subtotal: I^2 = 10.3%; P = 0.34	1.79 (1.50–2.13)	415/2935	200/2624
Galantamine			
Brodaty et al, 2005* (128)	1.61 (0.94–2.78)	52/645	16/320
Bullock et al, 2004* (129)	1.51 (0.89–2.57)	40/152	15/86
Erkinjuntti et al, 2002* (130)	2.44 (1.47–4.07)	79/396	16/196
Raskind et al, 2000* (132)	4.04 (2.46–6.63)	68/211	17/213
Rockwood et al, 2001* (133)	6.23 (2.57–15.07)	65/261	5/125
Tariot et al, 2000* (134)	1.41 (0.81–2.46)	27/273	20/286
Wilcock et al, 2000* (135)	2.02 (1.21–3.39)	39/218	19/215
Wilkinson and Murray, 2001* (136)	9.34 (3.85–22.67)	29/54	5/87
Auchus et al, 2007 (126)	1.97 (1.27–3.06)	54/397	27/391
Rockwood et al, 2006 (127)	2.58 (0.52–12.81)	5/64	2/66
Subtotal: I^2 = 67.5%; P = 0.001	2.50 (1.78–3.50)	458/2671	142/1985
Rivastigmine			
Agid et al, 1998* (142)	3.20 (1.21–8.48)	16/133	5/133
Corey-Bloom et al, 1998* (144)	4.26 (2.55–7.12)	67/231	16/235
Forette et al, 1999* (145)	5.33 (0.73–39.21)	10/45	1/24
Karaman et al, 2005* (146)	5.88 (0.32–107.49)	3/24	0/20
McKeith et al, 2000* (147)	1.03 (0.39–2.77)	7/59	7/61
Rösler et al, 1999* (149)	3.24 (1.94–5.41)	56/243	17/239
Winblad et al, 2007 (141)	1.58 (0.92–2.70)	78/996	15/302
Ballard et al, 2008 (138)	2.44 (1.47–4.05)	49/365	19/345
Feldman et al, 2007 (139)	1.51 (0.94–2.44)	62/455	20/222
Mok et al, 2007 (140)	2.00 (0.58–6.91)	6/20	3/20
Subtotal: I^2 = 44.6%; P = 0.062	2.35 (1.71–3.21)	354/2571	103/1601
Memantine			
Orgogozo et al, 2002* (155)	1.09 (0.65–1.83)	26/201	24/202
Peskind et al, 2006* (156)	1.77 (0.77–4.06)	15/165	8/156
Reisberg et al, 2003* (157)	0.62 (0.32–1.18)	13/126	21/126
Tariot et al, 2004* (158)	0.61 (0.34–1.11)	16/202	26/201
Wilcock et al, 2002* (159)	1.30 (0.75–2.26)	27/295	20/284
Bakchine and Loft, 2008 (150)	2.23 (0.94–5.27)	28/318	6/152
Porsteinsson et al, 2008 (152)	0.76 (0.38–1.53)	13/217	17/216
Saxton et al, 2012 (153)	0.71 (0.16–3.12)	3/136	4/129
Wilkinson et al, 2012 (154)	1.35 (0.66–2.78)	15/133	12/144
Subtotal: I^2 = 35.2%; P = 0.136	1.03 (0.77–1.38)	156/1793	138/1610

Weights are from random-effects analysis. AChEI = acetylcholinesterase inhibitor; RR = relative risk.
* Included in the systematic review by Raina and colleagues, 2008 (14).

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (simvastatin and atorvastatin) ($k = 4$; $n = 1153$), nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, indomethacin, and celecoxib) ($k = 4$; $n = 959$), gonadal steroids (estrogen with or without progesterone and testosterone) ($k = 5$; $n = 295$), and dietary supplements (multivitamins, B vitamins, vitamin E with or without vitamin C, and ω-3 fatty acids) ($k = 12$; $n = 2608$) (**Appendix Table 3**). None of the trials found a benefit for any of the medications or supplements on cognitive or physical function in persons with mild to moderate dementia or MCI (**Table 4** of the **Supplement**).

Caregiver Interventions

We identified 59 trials ($n = 8932$) representing a wide variety of interventions that targeted the caregiver or the caregiver–patient dyad with the primary aim of improving caregiver outcomes or skills (41, 42, 186–241). Most of the trials ($k = 52$; $n = 8103$) evaluated interventions with some type of psychoeducational component (that is, one that provided information about dementia or caregiving and sought to increase caregiver skills) (**Appendix Table 3** and **Table 5** of the **Supplement**). Other trials evaluated interventions that provided little or no dementia education or caregiver skill development but instead involved peer support only ($k = 4$; $n = 644$) (191, 235–237), physical activity for caregivers ($k = 3$; $n = 293$) (238–240), or an assessment and treatment plan development ($k = 1$; $n = 50$) (234).

Most of the psychoeducational trials reported at least caregiver burden ($k = 29$; $n = 4598$) or caregiver depression ($k = 34$; $n = 5423$) outcomes. Although there were substantial clinical differences among interventions evaluated and significant statistical heterogeneity among these trials, overall there was a generally consistent finding of small benefit on caregiver burden and caregiver depression outcomes in persons caring for patients with moderate dementia. Pooled analyses of 24 trials ($n = 2679$) showed a small but statistically significant effect (standardized mean difference, −0.23 [CI, −0.35 to −0.12]; $I^2 = 52.7\%$) on caregiver burden (**Figure 4**). Most studies reported 0- to 5-point group differences on the 88-item Zarit Caregiver Burden Interview. Likewise, pooled analyses of 30 trials ($n = 3537$) showed a small but statistically significant effect (standardized mean difference, −0.21 [CI, −0.30 to −0.13]; $I^2 = 34.1\%$) on caregiver depression (**Figure 5**). Most trials reported an approximate 2- to 5-point difference between groups on the 60-point Center for Epidemiologic Studies Depression Scale. The clinical meaning of these changes in caregiver burden and depression was, on average, probably small at best. Our ability to interpret the clinical importance and consistency of findings for other self-reported caregiver outcomes (for example, global stress or distress, anxiety, health-related quality of life [HRQL], or self-reported health status) and institutionalization was limited by sparse reporting of these outcomes. Only 1 of the included trials mentioned harms, and it found no adverse events in either group.

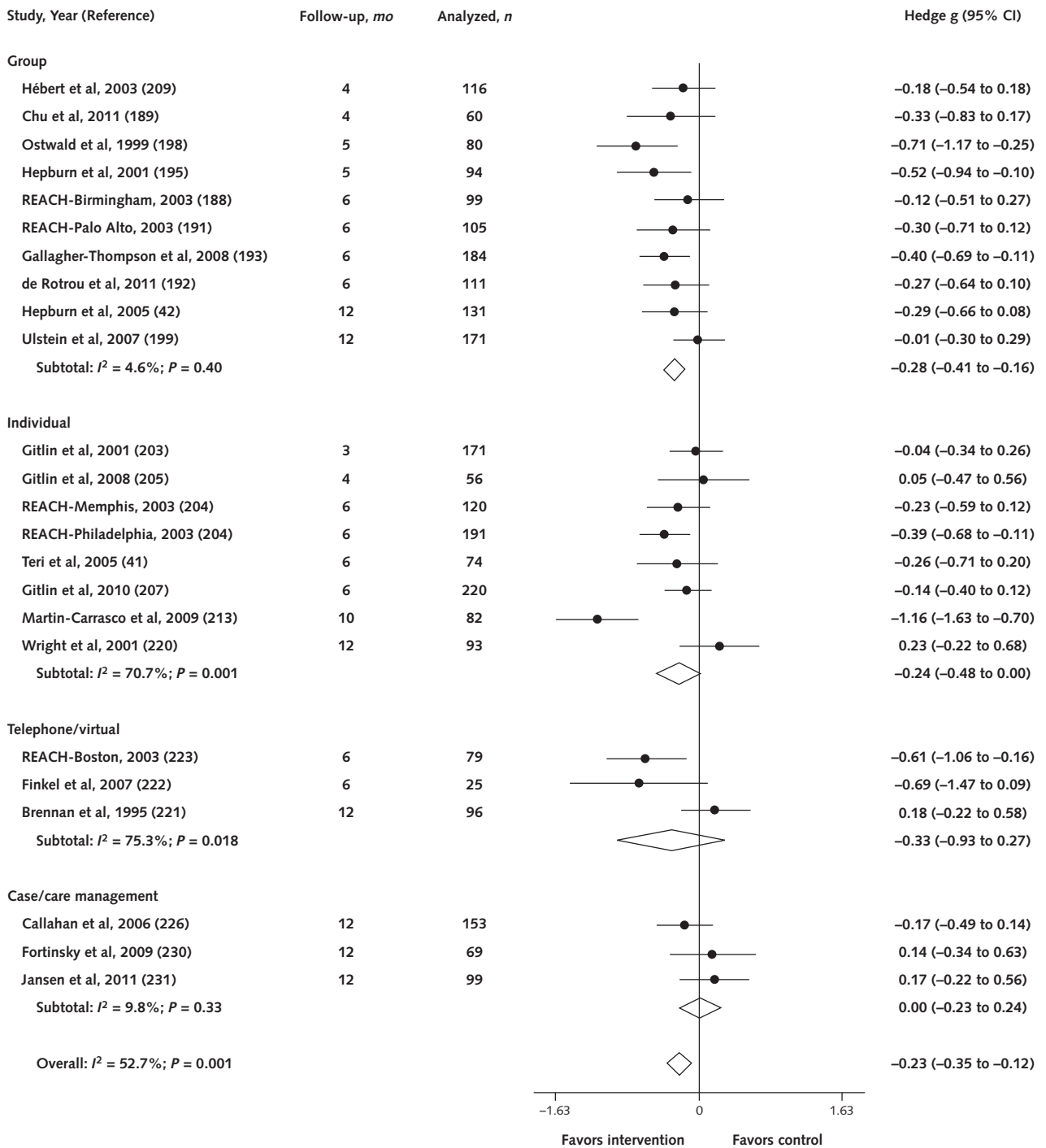
Nonpharmacologic Interventions Aimed at the Patient

We identified 32 trials ($n = 5662$) that evaluated nonpharmacologic interventions that targeted the patient rather than the caregiver or patient–caregiver dyad (104, 242–272). These included cognitive training, rehabilitation, or stimulation with or without motor skills training ($k = 15$; $n = 1128$); exercise interventions ($k = 10$; $n = 1033$); multidisciplinary care interventions involving assessment and care coordination ($k = 5$; $n = 1766$); and education-only intervention ($k = 2$; $n = 741$) (**Appendix Table 3** and **Table 6** of the **Supplement**). Although findings were inconsistent across 15 cognitive intervention trials, cognitive stimulation with or without cognitive training ($k = 6$; $n = 513$) seemed to improve global cognitive function at 6 to 12 months for persons with MCI or dementia (**Appendix Table 3**). A meta-analysis of these trials showed a moderate standardized effect size for global cognitive functioning favoring the intervention (−0.59 [CI, −0.93 to −0.25]; $I^2 = 52.7\%$). The 3 trials that included cognitive stimulation reported a wide range of differences in means, with a range of approximately 0 to 13 points on the ADAS-cog between the intervention and control groups (104, 243, 296). The 2 trials that used the MMSE differed by approximately 1 point between groups (244, 250). However, the limited number of trials, the clinical and statistical heterogeneity, and the wide CIs (ranging from not clinically meaningful to a large effect) limited our ability to determine the consistency of this benefit. Other important outcomes (for example, physical function, HRQL, and symptoms) were sparsely reported. None of the included trials reported harms. We did not identify any additional studies that explicitly evaluated harms of cognitive interventions.

Ten mostly fair-quality exercise trials showed no consistent benefit on cognitive outcomes and no benefit on patient depression outcomes (**Appendix Table 3** and **Table 6** of the **Supplement**). Other self-reported outcomes (for example, physical function and HRQL) and institutionalization were not commonly reported. Two trials of a multicomponent self-guided exercise intervention ($n = 220$) in persons with MCI found a small benefit in global cognitive function (approximately 1 point on the MMSE or ADAS-cog) at 12 to 18 months (258, 261). Although there was evidence of a benefit in a few of the better-conducted trials, we were unable to determine whether there is a clinically important benefit for exercise interventions on reported outcomes because of the limited number of trials and clinical heterogeneity of the populations, exercise interventions, and reported outcomes. We found no evidence of increased total or serious adverse effects due to exercise interventions among trial participants (258–260, 264).

Five trials evaluating different multidisciplinary care interventions found no benefit in cognitive or physical

Figure 4. **Meta-analyses of effects of psychoeducational caregiver interventions on caregiver burden.**



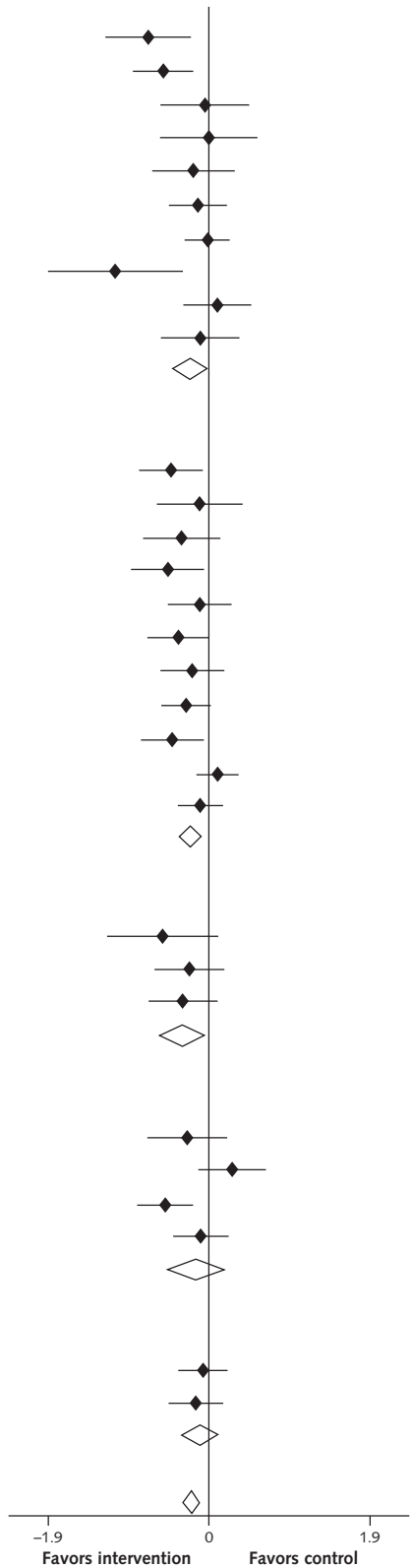
Weights are from random-effects analysis. REACH = Resources for Enhancing Alzheimer's Caregiver Health.

function, HRQL, or institutionalization (Table 6 of the **Supplement**). Two trials evaluating educational interventions aimed at residential care staff or clinicians caring for persons with dementia showed no benefits in reported outcomes (**Table 6** of the **Supplement**).

Discussion

Despite a large body of well-conducted diagnostic accuracy studies, only a handful of instruments have been studied in more than 1 study applicable to primary care. Although the MMSE is the best-studied instrument, it has

Figure 5. **Meta-analyses of effects of psychoeducational caregiver interventions on caregiver depression.**



Study, Year (Reference)	Follow-up, *mo*	Analyzed, *n*	Hedge g (95% CI)
Individual			
Chang, 1999 (201)	3	65	–0.72 (–1.22 to –0.23)
Graff et al, 2006 (208)	3	132	–0.55 (–0.89 to –0.20)
Gitlin et al, 2008 (205)	4	56	–0.05 (–0.57 to 0.46)
Martin-Cook et al, 2005 (214)	4	47	–0.01 (–0.57 to 0.56)
Teri et al, 2005 (41)	6	66	–0.19 (–0.67 to 0.29)
REACH-Memphis, 2003 (204)	6	140	–0.14 (–0.47 to 0.19)
REACH-Philadelphia, 2003 (204)	6	233	–0.02 (–0.28 to 0.23)
Marriott et al, 2000 (212)	12	27	–1.11 (–1.90 to –0.32)
Voigt-Radloff et al, 2011 (218)	12	98	0.09 (–0.30 to 0.49)
Wright et al, 2001 (220)	12	93	–0.11 (–0.56 to 0.34)
Subtotal: I^2 = 50.9%; *P* = 0.031			–0.23 (–0.42 to –0.03)
Group			
Losada et al, 2011 (197)	3	118	–0.45 (–0.82 to –0.08)
Chu et al, 2011 (189)	4	60	–0.12 (–0.62 to 0.38)
Ostwald et al, 1999 (198)	5	81	–0.33 (–0.78 to 0.12)
Hepburn et al, 2001 (195)	5	94	–0.49 (–0.92 to –0.07)
REACH-Palo Alto, 2003 (191)	6	132	–0.11 (–0.48 to 0.26)
REACH-Birmingham, 2003 (188)	6	121	–0.37 (–0.72 to –0.01)
de Rotrou et al, 2011 (192)	6	111	–0.20 (–0.57 to 0.17)
Gallagher-Thompson et al, 2008 (193)	6	195	–0.28 (–0.56 to 0.01)
Coon et al, 2003 (190)	7	130	–0.44 (–0.81 to –0.08)
Waldorff et al, 2012 (200)	12	271	0.10 (–0.14 to 0.33)
Kurz et al, 2010 (196)	15	221	–0.11 (–0.37 to 0.15)
Subtotal: I^2 = 26.0%; *P* = 0.196			–0.22 (–0.34 to –0.10)
Telephone/virtual			
Finkel et al, 2007 (222)	6	25	–0.55 (–1.20 to 0.10)
REACH-Boston, 2003 (223)	6	95	–0.24 (–0.64 to 0.16)
Brennan et al, 1995 (221)	12	96	–0.32 (–0.71 to 0.08)
Subtotal: I^2 = 0.0%; *P* = 0.73			–0.32 (–0.58 to –0.06)
Case/care management			
Fortinsky et al, 2009 (230)	12	74	–0.26 (–0.72 to 0.20)
Jansen et al, 2011 (231)	12	99	0.27 (–0.12 to 0.66)
Bass et al, 2003 (241)	12	157	–0.52 (–0.85 to –0.20)
Callahan et al, 2006 (226)	12	153	–0.11 (–0.42 to 0.21)
Subtotal: I^2 = 69.3%; *P* = 0.021			–0.16 (–0.49 to 0.17)
Family			
Joling et al, 2012 (224)	12	192	–0.08 (–0.36 to 0.20)
Mittelman et al, 2008 (225)	24	155	–0.16 (–0.47 to 0.15)
Subtotal: I^2 = 0.0%; *P* = 0.70			–0.11 (–0.32 to 0.10)
Overall: I^2 = 34.1%; *P* = 0.037			–0.21 (–0.30 to –0.13)

Weights are from random-effects analysis. REACH = Resources for Enhancing Alzheimer's Caregiver Health.

the longest administration time and is not available for public use without cost. Other publicly available instruments that have been studied in primary care–relevant populations can have adequate test performance, including the CDT, Mini-Cog, MIS, AMT, SPMSQ, FCSRT, 7MS, and IQCODE. However, the AMT, SPMSQ, FCSRT, and 7MS have limited evidence, and each has been studied only once in English. Although other instruments seem to have adequate test performance (such as the 6-Item Screener, Visual Association Test, General Practitioner Assessment of Cognition, ADL/IADL, Benton Orientation Test, Delayed Recall Test, and Short Concord Informant Dementia Scale), each of them has been studied only once in primary care–relevant populations. Our review of the diagnostic accuracy of screening for dementia includes twice the number of studies in existing reviews but is generally consistent with the findings of others (3, 69, 297, 298).

We found no studies to substantiate or refute concerns about harms of screening. Although screening and the subsequent diagnostic work-up for abnormal results are noninvasive, false-positive results could represent a harm if patients or clinicians do not follow through with subsequent diagnostic testing and falsely assign a diagnosis of dementia. If false-positive results are a concern, instruments or cut points with high specificity should be given preference. Potential harms from false-negative results, if they are of concern, can be minimized with repeated screening.

Although screening for cognitive impairment can identify persons with dementia, there is no empirical evidence on whether interventions affect clinician, patient, or family decision making. Caregiver interventions and FDA-approved medications for AD show a small benefit for patients and caregivers, although the clinical importance of this benefit is unclear, especially in persons with screen-detected cognitive impairment or those with MCI or mild dementia. Acetylcholinesterase inhibitors and memantine can improve global cognitive function, and AChEIs can improve short-term global function for patients with moderate AD. The average effects of changes in cognitive functioning observed in trials are small, and the clinical importance of population benefits is probably negligible when commonly accepted thresholds are used. This small benefit of AChEIs must be balanced by the common adverse effects. Because of resource limitations, we did not search the FDA Web site or contact industry for unpublished data. A review of trial registry data suggested that 2 trials in persons with MCI (ClinicalTrials.gov, NCT00236574 and NCT00236431) were stopped early because of interim analyses suggesting increased mortality in persons receiving galantamine compared with those receiving placebo. Our review's findings are consistent with those of other similar systematic reviews and guidelines (14, 299, 300).

Likewise, complex interventions aimed at caregivers and dyads can reduce caregiver burden and depression, but the average effects in these trials were small. Only half of the trials of caregiver interventions were conducted in the United States, and availability of these complex interventions in the United States is limited. Our review is generally consistent with existing systematic reviews except for slight differences in the magnitude of effect on caregiver outcomes due to differences in included trials and definitions of outcomes (301–305).

Other interventions (for example, cognitive stimulation or exercise) have limited evidence to support use in persons with MCI or mild to moderate dementia. Although our review's findings are promising, the certainty and magnitude of effect of cognitive stimulation in persons with mild to moderate dementia or MCI are still unclear. Findings from existing systematic reviews evaluating cognitive interventions were generally consistent with those of our review (306–308), although 1 comprehensive Cochrane review that included persons with any stage of dementia and institutionalized individuals found more consistent and precise findings of benefit on cognitive function (306). Although no consistent benefit was observed for exercise interventions, 3 of the better-conducted trials suggested a benefit in global cognitive function or physical functioning and HRQL, consistent with another existing systematic review's findings in noninstitutionalized older adults with dementia (309).

Because of this narrow scope, our review does not address several important aspects of screening test performance, including the psychometric properties of testing other than sensitivity and specificity, the validation of screening instruments in different languages, the optimum cut points in scoring the included instruments, the differential ability of instruments to detect different types of dementia, the comparative performance of screening instruments, and the ability to improve diagnostic performance by combining screening instruments. Our review of treatments focuses only on the benefits and harms in a subset of persons with mild to moderate dementia or MCI and does not address the comparative effectiveness of different types of interventions or the minimum necessary components for the effectiveness of complex interventions.

Expert consensus guidelines state that early detection of cognitive decline may be beneficial because clinicians can optimize medical management, offer relief based on better understanding of symptoms, maximize decision-making autonomy and planning for the future, and offer appropriate access to services that will ultimately improve patient outcomes and reduce future costs (310). Although this is a logical argument, there is little or no empirical evidence to support it. How and whether clinician decision making and patient and family decision making are affected by earlier identification of cognitive impairment or earlier management of patients with dementia and their caregivers are important aspects of management of this rapidly growing health care problem. Important patient outcomes, such as global functioning, HRQL, global physical functioning, emergent or unexpected health care utili-

zation, and institutionalizations, are inconsistently reported but crucial to understanding the true balance of benefits and harms for patients and caregivers, especially in light of small, clinically uncertain benefits seen on continuous measures of cognitive function or caregiver burden.

On the basis of empirical evidence, how best to apply brief cognitive assessment tools to aid in the identification of dementia (population-based screening vs. more targeted approaches suggested by Medicare's Annual Wellness Visit) is still unclear. To operationalize the Annual Wellness Visit's mandate to assess for cognitive impairment, experts have suggested a stepwise approach to identifying persons to whom a brief cognitive instrument should be applied. Research comparing which criteria (for example, age, comorbid conditions, or functional status) should lead primary care clinicians to perform cognitive assessment is much needed. Additional evaluation of brief instruments in more representative populations is needed after initial validation studies to establish reproducibility and to understand population and scoring differences that may lead to important variation in test performance. The harms of screening are poorly studied. Some have argued that these harms are minimal, whereas others contend that the harms of screening and mislabeling persons with dementia are real given the variation in practice of diagnostic confirmation of disease. If broader adoption of screening for cognitive impairment is implemented, it would be wise to better understand these tradeoffs.

Clinical research around defining, diagnosing, and treating cognitive impairment before the loss of independence with IADLs is rapidly evolving. Experts in this field are working to refine diagnostic criteria and to standardize the identification of persons with MCI or "mild neurocognitive disorder," as it is called in the DSM-V. Future research should focus on improved criteria and subtypes of MCI with demonstrated prognostic and predictive value. Criteria with established predictive value should then be operationalized in a standardized fashion in research studies.

Although it is clear that brief instruments to screen for cognitive impairment can adequately detect dementia, there is no empirical evidence that screening for or early diagnosis of cognitive impairment improves decision-making or important patient, caregiver, or societal outcomes. Despite a large body of evidence spanning decades of research, it is still unclear whether FDA-approved medications, caregiver interventions, cognitive interventions, or exercise interventions in persons with earlier detected cognitive impairment have a clinically significant effect. How best to identify persons with cognitive impairment and understanding how and whether early identification affects important decision making is much needed to address this common, growing, and costly health condition.

From Kaiser Permanente Northwest and Oregon Health & Science University, Portland, Oregon, and HealthPartners Institute for Education and Research, Bloomington, Minnesota.

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Current author addresses and author contributions are available at www.annals.org.

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References are available at www.annals.org.

Current Author Addresses: Drs. Lin and O'Connor and Ms. Perdue: Kaiser Permanente Center for Health Research Northwest, 3800 North Interstate Avenue, Portland, OR 97227.
Dr. Rossom: HealthPartners, 8170 33rd Avenue South, Minneapolis, MN 55440.
Dr. Eckstrom: Oregon Health & Science University, 3181 SW Sam Jackson Parkway, Department of Medicine L475, Portland, OR 97239.

Author Contributions: Conception and design: J.S. Lin, E. Eckstrom.
Analysis and interpretation of the data: J.S. Lin, E. O'Connor, R.C. Rossom, L.A. Perdue, E. Eckstrom.
Drafting of the article: J.S. Lin, E. O'Connor, R.C. Rossom.
Critical revision of the article for important intellectual content: J.S. Lin, E. O'Connor, R.C. Rossom, E. Eckstrom.
Final approval of the article: J.S. Lin, E. O'Connor, R.C. Rossom, L.A. Perdue, E. Eckstrom.
Statistical expertise: E. O'Connor.
Administrative, technical, or logistic support: L.A. Perdue.
Collection and assembly of data: J.S. Lin, E. O'Connor, R.C. Rossom, L.A. Perdue, E. Eckstrom.

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Appendix Table 1. Inclusion Criteria

Key Question	Criteria
1–3 (screening)	Community-dwelling older adults (including persons in senior communities, assisted living facilities, and adult foster care), excluding populations referred or selected for cognitive impairment (including memory clinics, psychogeriatric clinics, and AD research centers). Brief screening instrument (administration time ≤10 min or can be self-administered in ≤20 min). Any decision-making outcomes (patient, family, or clinician), patient health or safety outcomes, family or caregiver burden or health outcomes, or societal outcomes (KQ 1); diagnostic accuracy (sensitivity and specificity for dementia or MCI) outcomes (KQ 2); or harms (unwanted or unexpected direction of effect on health outcomes, psychological harms, harms due to labeling, or poor adherence to diagnostic follow-up) (KQ 3) Screening studies of efficacy limited to trials (KQ 1); diagnostic accuracy studies, excluding case–control studies (KQ 2)*; and any study design for harms of screening (KQ 3).
4–5 (treatment)	Treatment and management of MCI or mild to moderate dementia. Pharmacologic interventions, including FDA-approved medications used to treat patients with AD to prevent or delay cognitive decline (i.e., donepezil, galantamine, rivastigmine, and memantine) and medications primarily aimed at cardiovascular risk reduction for treatment of VaD, including antiplatelet medication, antihypertensive medication, and HMG-CoA reductase inhibitors; NSAIDs; gonadal steroids (i.e., estrogen, progesterone, and testosterone); and dietary supplements (i.e., vitamins, minerals, and antioxidants). Nonpharmacologic interventions aimed at patients or their nonprofessional caregivers, including multicomponent, support-only, education-only, exercise, or cognitive interventions and excluding interventions primarily aimed at noncognitive symptom management (e.g., music therapy, light therapy, or nighttime home monitoring systems) and respite care or day care interventions. Any decision-making outcomes (e.g., health care planning, including advance directives, screening and diagnostic decisions, safety planning, or legal and financial planning), patient health or safety outcomes (e.g., cognitive function, physical function, overall function, HRQL, safety, medication use or adherence, neuropsychiatric symptoms [e.g., insomnia, depression, agitation, aggression, or wandering], emergency department use, hospitalizations, or institutionalization), caregiver outcomes (e.g., caregiver burden or HRQL), or societal outcomes (e.g., automobile accidents). Treatment studies of efficacy were limited to good-quality systematic reviews of trials or trials with a true control group (KQ 4); harms studies included all trials that were included for KQ 4, open-label extensions of included drug trials, and large cohort or case–control studies ($n \geq 1000$) (KQ 5).

AD = Alzheimer disease; FDA = U.S. Food and Drug Administration; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; HRQL = health-related quality of life; KQ = key question; MCI = mild cognitive impairment; NSAID = nonsteroidal anti-inflammatory drug; VaD = vascular dementia.
* We excluded case–control diagnostic accuracy studies in which patients were selected on the basis of having known dementia or MCI. Distorted selection of patients in selective recruitment or case–control designs has repeatedly been shown to overestimate sensitivity due to spectrum bias (23–27).

Appendix Table 2. Diagnostic Accuracy of Brief Cognitive Screening Instruments in Primary Care for Dementia

Instrument (Reference)	Studies, *n*	Participants, *n*	Quality	Sensitivity Range (95% CI)	Specificity Range (95% CI)	Consistency	Applicability
Very brief (≤5 min)							
CDT (50–55, 77)	6*	2170	Fair	67–97.9 (39–100)	69–94.2 (54–97.1)	Inconsistency may be due to difference in population or scoring methods.	Wide range of prevalence; unclear optimum scoring.
Mini-Cog (50, 56–58)	4	1570	Fair	76–100 (54–100)	54–85.2 (43–88.4)	Inconsistency may be due to difference in population or scoring methods.	Wide range of prevalence; unclear optimum cut point.
MIS or MIS-T (54, 56, 59–61)	5	1971	Fair	43–86 (24–96)	93–97 (56–100)	2 best-quality studies with low sensitivities.	Wide range of prevalence.
MSQ or SPMSQ (53, 62–64)	4	1057	Fair	92.3–100 (29–100)	86.5–100 (76–100)	Inconsistency may be due to cut points.	Wide range of prevalence; only 1 study in English; unclear optimum cut point.
Verbal fluency (50, 53, 54, 59, 65, 77)	6	2083	Fair	37–89.5 (19–100)	43–97 (33–99)	Test performance overlapped regardless of cut point.	Wide range of prevalence.
Cut point of 12 or 13 points (50, 54, 59)	3	1041	–	37–89.5 (19–100)	62–97 (48–99)	–	–
Cut point of 14 or 15 points (54, 59, 65)	3	905	–	57–88 (35–NR)	43–94 (33–97)	–	–
Brief (6–10 min)							
MMSE† (51, 57, 62, 63, 65–84, 88)	14‡	10 185	Fair	88.3§ (81.3–92.9)	86.2§ (81.8–89.7)	Test performance overlapped regardless of cut point.	Wide range of prevalence and languages; optimum cut point for low education is lower.
AMT (63, 66, 80, 81)	4	824	Fair	42–100 (16–100)	83–95.4 (76–99)	Unclear whether inconsistency due to difference in populations.	Wide range of prevalence; only 1 study in English (none in United States).
FCSRT (53, 54)	2	734	Fair	86–100 (41–100)	73–87.2 (56–96)	Only 2 studies; different populations and cut points.	Only 1 study in English; unclear optimum cut point.
7MS (53, 85)	2	553	Fair	66.7–100 (NR–100)	95.1–100 (86.8–100)	Only 2 studies; different populations and cut points.	Only 1 study in English; unclear optimum cut point.
TICS (59, 86)	2	677	Fair	74–88 (54–96)	86–97 (81–91)	Only 2 studies; different populations and cut points.	Only 1 study in English; unclear optimum cut point.
Self-administered (≤20 min)							
IQCODE (54, 68, 74, 79, 87)	5	1251	Fair	75–87.6 (41–100)	65–91.1 (59–100)	Test performance overlapped for different cut points.	Unclear optimum cut point; cut point recommended by test developers not supported by evidence.

7MS = 7-Minute Screen; AMT = Abbreviated Mental Test; CDT = Clock Drawing Test; FCSRT = Free and Cued Selective Reminding Test; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; MIS = Memory Impairment Screen; MIS-T = Memory Impairment Screen by Telephone; MMSE = Mini-Mental State Examination; MSQ = Mental Status Questionnaire; NR = not reported; SPMSQ = Short Portable Mental Status Questionnaire; TICS = Telephone Interview for Cognitive Status.

* Six of 7 included studies reported sensitivity and specificity.

† Cut point of 23 of 24 points or 24 of 25 points.

‡ Fourteen of 25 included studies reported sensitivity and specificity at these specific cut points.

§ Pooled analysis.

Appendix Table 3. **Benefits and Harms of Interventions for Mild to Moderate Dementia and MCI**

Intervention (Reference)	Studies, *n*	Participants, *n*	Quality	Summary of Findings	Consistency	Applicability
Effectiveness of pharmacologic interventions						
AChEIs (102–149)	48	18 390	Fair	Donepezil (k = 24; n = 7553), galantamine (k = 12; n = 6008), and rivastigmine (k = 12; n = 4829) had statistically significant benefits on global cognitive function in the short term (change of approximately 1 to 3 points on the ADAS-cog). In a subset of trials, donepezil, galantamine, and rivastigmine had a small benefit on global function, as measured using the CIBIC-plus, in the short term. Physical function was only reported in half of the trials and showed mixed results. Only 4 trials (3 for donepezil and 1 for galantamine) in MCI were found. Although small, statistically significant benefits were shown for donepezil: 2 trials showed no difference in progression of MCI to dementia at 3 y.	Generally consistent findings of benefit for cognitive and global function outcomes. Inconsistent findings on physical function; cannot evaluate inconsistency given sparse reporting.	Most trials in moderate dementia, primarily AD (few trials in VaD); few trials in MCI; populations primarily from North America and western Europe; doses of medications applicable to common use.
Memantine (150–159)	10	3465	Fair	Statistically significant but clinically marginal benefits in cognitive function in the short term (k = 9; n = 3323) were found. Benefits were mixed in global (k = 7; n = 1880) and physical (k = 5; n = 1962) function. Benefits seemed to be limited to persons with moderate AD.	Consistent findings in global cognitive function. Inconsistent findings of benefit in global function and physical function. Cannot determine whether differences in population or study characteristics explain inconsistencies.	Most trials in moderate dementia, primarily AD (2 trials in VaD); populations from North America and western Europe; doses of medications applicable to common use.
Aspirin (160, 161)	2	459	Fair	No benefit was found in global cognitive or physical function for low-dose aspirin.	Consistent finding of no benefit.	Mild to moderate dementia and MCI, primarily AD; populations from United States and western Europe; low-dose aspirin.
HMG-CoA reductase inhibitors (162–165)	4	1153	Fair	No benefit was found in global cognitive function, physical function, or neuropsychiatric symptoms for simvastatin or atorvastatin.	Consistent finding of no benefit.	Mild to moderate dementia, primarily AD; populations from United States and western Europe; doses of medications applicable to common use.
NSAIDs (166–169)	4	959	Fair	No benefit was found in global cognitive or physical function for ibuprofen, naproxen, indomethacin, or celecoxib. Other outcomes were sparsely reported.	Consistent finding of no benefit regardless of type of NSAID.	Mild to moderate dementia; populations from United States and western Europe; doses of medications applicable to common use.
Gonadal steroids (170–174)	5	295	Fair	No benefit was found in global cognitive or physical function for estrogen with or without progesterone (k = 4; n = 277). No benefit was found in global cognitive function for testosterone (k = 1; n = 18). Other outcomes were sparsely reported.	Consistent finding of no benefit regardless of type of hormone.	Mild to moderate dementia, only in AD; populations from United States, Europe, and Asia; doses of medications applicable to common use.
Dietary supplements (161, 175–185)	12	2608	Fair	No benefit was found in global cognitive or physical function for dietary supplements, including multivitamins (k = 1; n = 89), B vitamins (k = 7; n = 1294), vitamin E with or without vitamin C (k = 3; n = 522), or ω-3 fatty acids (k = 4; n = 1145). Other outcomes were sparsely reported.	Consistent finding of no benefit regardless of type of dietary supplement.	Mild to moderate dementia and MCI, primarily AD; populations from United States, northern Europe, and Asia.

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Appendix Table 3—**Continued**

Intervention (Reference)	Studies, *n*	Participants, *n*	Quality	Summary of Findings	Consistency	Applicability
Effectiveness of nonpharmacologic interventions						
Caregiver (or dyad) interventions (41, 42, 186–241)	59	8932	Fair	Most trials evaluated caregiver interventions with a psychoeducational component. Small to very small benefit was found in caregiver burden and caregiver depression for a broad range of caregiver interventions with a psychoeducational component in the short term (generally 3 to 12 mo). Pooled analyses for caregiver burden (k = 24; n = 2679) and depression (k = 30; n = 3537) outcomes showed a small benefit (caregiver burden SMD, −0.23 [95% CI, −0.35 to −0.12]; I^2 = 52.7%; depression SMD, −0.21 [CI, −0.30 to −0.13]; I^2 = 34.1). Other outcomes were sparsely reported.	Generally consistent for caregiver burden and depression outcomes; large clinical and statistical heterogeneity of interventions limits interpretation of point estimates from pooled analyses.	Most trials in moderate dementia; populations from North America, Europe, Australia, and Asia; wide range of types and intensities of interventions.
Cognitive training, rehabilitation, or stimulation, with or without motor training (104, 242–255)	15	1128	Fair	Cognitive interventions had inconsistent findings of benefit. Cognitive stimulation with or without cognitive training can improve cognitive function in persons with MCI or mild dementia. Pooled analyses for global cognitive outcomes (k = 6; n = 513) showed a moderate benefit at 6 to 12 mo (SMD, −0.59 [CI, −0.93 to −0.25]; I^2 = 52.7%). Because CIs were wide, the effect on global cognitive functioning could range from very small to moderate. Other outcomes were sparsely reported.	Unclear whether inconsistency in findings for cognitive function was due to differences in study quality, populations, intervention type or intensity, or outcomes measured.	Mild to moderate dementia and MCI; populations in North America, Europe, and Australia.
Exercise interventions (256–265)	10	1033	Fair	Findings about benefit from exercise interventions were inconsistent. However, some well-conducted studies suggest small benefits in cognitive function in persons with MCI (k = 2; n = 220) and in physical function and HRQL in persons with dementia (k = 1; n = 153). Other outcomes were sparsely reported.	Inconsistent; unclear whether inconsistency due to differences in study quality, population, intervention, or outcomes measured.	Mild to moderate dementia and MCI; populations in North America, Australia, and Hong Kong.
Multidisciplinary interventions (266–270)	5	1766	Fair	Multidisciplinary care interventions involving assessment and care coordination showed no benefit in global cognitive function, physical function, institutionalization, or HRQL.	Consistent finding of no benefit.	Mild to moderate dementia or MCI; only 1 trial in the United States (done in an assisted living facility); remaining trials done in Europe.
Education only (271, 272)	2	741	Fair	Two trials aimed at educating residential care staff and/or GPs treating persons with dementia found no benefit to HRQL, neuropsychiatric disturbances, hospitalization, or institutionalization.	Consistent finding of no benefit.	Persons with mild to moderate dementia living in residential care facility in Australia; GP practices in Germany.

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Appendix Table 3—**Continued**

Intervention (Reference)	Studies, *n*	Participants, *n*	Quality	Summary of Findings	Consistency	Applicability
Harms of interventions with evidence of benefit						
Pharmacologic interventions (102, 103, 105–107, 109–114, 116–130, 132–136, 138–142, 144–147, 149–159, 273–287, 289, 290, 292, 293, 311)	71	228 155	Fair	Discontinuation from AChEI (k = 45), but not memantine (k = 12), was more common than from placebo. Across trials, there did not seem to be a difference in total serious adverse events for any of these medications. Observational studies examining AChEIs (k = 13; n = 197 811) suggest that the most common serious adverse events are CNS, heart rate/rhythm, and gastrointestinal disorders and that bradycardia and adverse events related to bradycardia (e.g., fall or syncope) are increased with their use.	Generally consistent findings by drug class effect; estimation of frequency of adverse events may be higher in observational studies because of population selection.	Mild to moderate dementia and MCI; populations from North America, Europe, Australia, and Asia.
Nonpharmacologic interventions (258–260, 264)	4	439	Fair	Harms were not reported for caregiver or cognitive interventions. There was no evidence of increased total or serious adverse effects due to exercise interventions.	Few hypothesized harms; however, unclear consistency given that adverse effects were rarely reported.	Mild to moderate dementia and MCI; populations restricted to trial populations.

AChEI = acetylcholinesterase inhibitor; AD = Alzheimer disease; ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; CIBIC-plus = Clinician Interview-Based Impression of Change Plus Caregiver Input; CNS = central nervous system; GP = general practitioner; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; HRQL = health-related quality of life; MCI = mild cognitive impairment; NSAID = nonsteroidal anti-inflammatory drug; SMD = standardized mean difference; VaD = vascular dementia.