Screening for Dementia in Primary Care: A Summary of the Evidence for the U.S. Preventive Services Task Force

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Epidemiology

Dementia is an acquired syndrome of decline in memory and at least one other cognitive domain, such as language, visuo-spatial, or executive function, sufficient to interfere with social or occupational functioning in an alert person.[1] Multiple diseases can cause the dementia syndrome (hereafter, dementia). Alzheimer's disease and cerebrovascular ischemia (vascular dementia) are the 2 most common causes; some cases involve both of these etiologies. Although some potentially reversible conditions, such as hypothyroidism or vitamin B-12 deficiency, are often considered to be causes of dementia, no more than 1.5% of cases of mild to moderate dementia are fully reversible.[2]

Age is the best studied and the strongest risk factor for dementia. Risk factors for Alzheimer's disease, other than age, include having a first-degree relative with a history of Alzheimer's disease and the apolipoprotein E-ε4 (APOE-ε4) genotype.[3–5] Cardiovascular risk factors such as hypertension are associated with an increased risk of both Alzheimer's disease and vascular dementia.[5–7]

The aging of the U.S. population has been accompanied by a dramatic increase in the prevalence of dementia. From 3% to 11% of people older than 65 and 25% to 47% of those older than 85 have dementia.[8–13] In 1997, the number of people with Alzheimer's disease in the United States was estimated to be 2.3 million, more than 90% of whom were aged 60 years and older.[14]

Dementia causes a high burden of suffering for patients, their families, and society.[15–21] For patients, it leads to increased dependency and complicates other comorbid conditions. For families, it leads to anxiety, depression, and increased time spent caring for a loved one. The annual societal cost of dementia is approximately $100 billion, from health care and related costs as well as lost wages for patients and family caregivers.[10, 16, 22]

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Clinicians using routine history and physical examination do not readily diagnose dementia during clinic visits. More than 50% of people with dementia have never been diagnosed by a physician, including many with mild but some with moderate dementia.[23–27] This raises the possibility that screening tests might be able to identify people with undiagnosed dementia, and therefore permit patients and their families to receive care at an earlier stage in the disease process. Given the low prevalence of reversible causes, a recommendation for screening will depend on evidence of the additional benefits of earlier treatment for persons with irreversible causes, primarily Alzheimer's disease and vascular dementia.

For dementia screening to lead to improved health outcomes, primary care providers would need to have a brief, accurate screening test to apply during routine office visits. A positive screening test would then result in a diagnostic interview and clinical examination based on the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (DSM IV) that could be performed by either the primary care physician or a specialist such as a geriatrician or neurologist. Finally, knowledge of the dementia diagnosis at this early stage would lead to improved health outcomes through more effective treatment. Ideal evidence to support these hypotheses would come from a randomized control trial (RCT) of screening and earlier intervention, with long-term follow-up for both adverse and beneficial effects of screening.

The 1996 *Guide to Clinical Preventive Services* from the U.S. Preventive Services Task Force (USPSTF) found insufficient evidence to recommend for or against screening for dementia.[28] Since the last USPSTF review, studies have been published concerning screening tests as well as both pharmacologic and caregiver interventions. Given the new evidence and the growing importance of this condition, the RTI-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) conducted a systematic review of the literature regarding the benefits and the harms of screening primary care populations to detect undiagnosed cases of dementia. Our review did not consider the issue of screening to detect people with cognitive impairment, termed "mild cognitive impairment" (MCI), who do not meet the criteria for dementia. Experts do not agree about the definition of MCI, and other reviews have not found evidence of effective treatment for people with this problem.[29,30]

Methods

Using USPSTF methods,[31] we developed an analytic framework and 8 key questions to guide our systematic review of the evidence for dementia screening. We developed eligibility criteria for selecting the evidence relevant to answer the key questions. We used the eligibility criteria to develop search terms and searched MEDLINE, PsycINFO, EMBASE, and the Cochrane Library databases for systematic reviews and high-quality studies relevant to each question. We limited all searches to reviews and studies published in English between January 1, 1994, and September 1, 2002, and that contained information relevant to a primary care population.

We searched first for studies of screening that provided direct evidence that screening improves cognitive, social, or physical function; number of hospitalizations, institutionalizations, or health care visits; behavioral problems; caregiver burden; accidental injuries such as falls or automobile crashes; or patients' overall health-related quality of life. Because we found no direct evidence connecting screening and improved health outcomes, we searched for indirect evidence of the benefit of screening, including the prevalence of undiagnosed dementia; the accuracy of screening tests; the efficacy of early pharmacologic and nonpharmacologic treatment for people with Alzheimer's disease and vascular dementia; caregiver intervention for people with dementia; and the efficacy of interventions targeted to caregivers. We also searched for evidence of the adverse effects of screening and treatment.

At least 2 authors reviewed abstracts and articles to identify those that met the eligibility criteria and then abstracted relevant information using standardized abstraction forms. We graded the quality of the included articles using criteria developed by the USPSTF Methods Work Group.[31] In all cases, we accepted either single studies or systematic reviews that addressed the key question, met eligibility criteria, and were rated of at least fair quality. Table 1 lists these criteria and the number of articles found meeting them for each question.

Table 1. Key questions, eligibility criteria, and number of articles meeting criteria

Key question	Eligibility criteria	Systematic reviews and additional studies not in systematic reviews
All	Published between 1/1/94 and 9/1/02 English language Human subjects, age ≥ 60 years MEDLINE, PsycINFO, EMBASE, Cochrane Library	
1. Direct evidence of screening	RCT of screening Health outcomes	Systematic reviews: 0 Additional studies: 0
2. Prevalence of undiagnosed dementia	Systematic reviews Cross-sectional prevalence Community or primary care setting Appropriate reference standard	Systematic reviews: 0 Additional studies: 4 [26,27,32,33]
3. Accuracy of screening tests	Systematic reviews; prospective cohorts Cross-sectional prevalence Community or primary care setting Appropriate reference standard	Systematic reviews: 1 [37] Additional studies: 9 [38–43,45,108,109]
4. Efficacy of pharmacologic treatment	Systematic reviews, RCTs Mild to moderate dementia Health outcomes	Systematic reviews: 12 [72–75,86,87,93,110–114] Additional Studies: 19 [76–85,88–90,92,115–119]
5. Efficacy of nonpharmacologic interventions for patients	Systematic reviews, RCTs Mild to moderate dementia Health outcomes	Systematic reviews: 0 Additional studies: 0
Efficacy of caregiver interventions	Systematic reviews, RCTs Mild to moderate dementia Health outcomes	Systematic review: 1 [96] Additional Studies: 6 [97,99–102,104*]
6. Efficacy of interventions for planning	Systematic reviews, RCTs Mild to moderate dementia Health outcomes	Systematic reviews: 0 Additional studies: 0
7. Harms of screening	Systematic reviews, RCTs Mild to moderate dementia Psychological or other health outcomes	Systematic reviews: 0 Additional studies: 0
8. Harms of treatment	Systematic reviews, RCTs Mild to moderate dementia Health outcomes	Systematic reviews: 4 [72–75] Additional studies: 5 [76–80]

Note: RCT indicates randomized, controlled trial.
* Two articles are combined because they both report the results of 1 study.

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Results

The best evidence for or against screening for dementia would be derived from a well-designed RCT of screening with health outcomes. No such trial has been completed. In the absence of such a trial, evidence for or against screening comes from studies of the prevalence of undiagnosed dementia, the accuracy of screening instruments, the efficacy of treatments for people with dementia detected by screening, and the harms of screening and treatment.

How Common Is Undiagnosed Dementia?

Three studies in primary care populations aged 65 years and older compared the frequency of dementia by standard diagnostic tests with medical record notation of dementia or cognitive impairment[26,27,32] or by independent questionnaire of the physician.[27] Among all primary care patients aged 65 and older, 3.2% to 12% met criteria for dementia but had no dementia documentation (Table 2) or knowledge by the physician. A population-based study found that the prevalence of undiagnosed dementia among individuals aged 65 years and older was 1.8%.[33] Another population-based study found that about half of reliable relatives of men with mild dementia failed to recognize a problem with thinking or memory.[34]

Undiagnosed patients accounted for 50% to 66% of all cases of dementia in the primary care populations studied; the majority of missed cases were mild to moderate. In one small study, 78.6% (11/14) of people with mild dementia, 71.4% (5/7) with moderate dementia, and 20% (1/5) with severe dementia had no medical record documentation of a dementia diagnosis.[27] New screening in primary care practice could, therefore, potentially double the number of patients diagnosed with dementia, and most newly discovered cases would have mild to moderate forms of the disease.

How Accurate Are the Screening Tests?

Three methodological problems make it difficult to assess the accuracy of screening tests for dementia. First, research has examined the accuracy of a large number of screening instruments to a limited degree. Few instruments have been examined in more than 2 or 3 small studies. Second, investigators used a variety of reference standards for the diagnosis of dementia. Because functions such as cognition are continuous, the reference standard must set the

Table 2. Estimates of undiagnosed dementia in primary care practices

Study, year	Setting	Age of patient population	Reference standard	Prevalence of undiagnosed dementia in all patients, %
Olafsdottir et al., 2000 [26]	Primary health center, Sweden	> 70 years	DSM-IIIR	12
Eefsting et al., 1996 [32]	Community and general practices, Netherlands	≥ 65 years	DSM-III	3.2
Valcour et al., 2000 [27]	General internal medicine clinic, Hawaii	≥ 65 years	DSM-IIIR	5.7
Sternberg et al., 2000 [33]	General, randomly sampled community, Canada	≥ 65 years	DSM-IIIR	1.8

Note: DSM-III indicates *Diagnostic and Statistical Manual of Mental Disorders*, third edition; DSM-IIIR, *Diagnostic and Statistical Manual of Mental Disorders*, third edition: revised.

point at which the diagnosis of dementia can be made. Where this point is set makes a large difference in evaluating screening tests.[35] Although research has yet to determine the optimal point for diagnosing dementia, the criteria of DSM IV are widely accepted in the United States and will be used as the standard in this review.[36] Third, the populations in the studies of screening instruments varied greatly. Many studies included participants with severe dementia or people from memory clinics; these people are not the focus of screening. Few studies have provided information on the accuracy of screening tests for detecting people with mild dementia. Thus, the evidence about test accuracy from these studies may be most appropriately extrapolated to detect people with moderate dementia; the accuracy of these tests in detecting people with mild dementia may be lower.

Although we examined many studies of screening tests, we included only studies that examined instruments that are feasible for use in primary care settings, used DSM-IV (or similar) criteria as the reference standard, and provided information about the test's characteristics among people who were not known by themselves or others to have symptoms of dementia.

Most screening tests for dementia can be divided into cognitive tests of patients and functional assessments using both patients and others as informants. In 1996, the Agency for Health Care Policy and Research (AHCPR) published a systematic review and meta-analysis of studies that evaluated dementia screening tools.[37] The review found 1 informant-based functional status instrument and 4 patient-based cognitive assessment tools, including the Mini-Mental Status Examination (MMSE), the most commonly used and studied test, which had acceptable accuracy (Table 3). Since that review, 8 additional studies have examined the MMSE with similar findings.[38–45] The sensitivity of these tests is in the range of approximately 69% to 90%, with specificity depending on the cutpoint used for an abnormal test (Table 3). Using a cutpoint to attain high sensitivity necessarily lowers specificity. The positive predictive value of a screening test in a population with a prevalence of undiagnosed dementia of 10% is generally about 40% to 50% for these tests (Table 3).

Several other patient-based cognitive screening tests have been tested either in single studies or in several studies that do not meet our criteria. Tests such as the Short Portable Mental Status Questionnaire,[46,47] the Clock Drawing Test,[48–52] the Modified Mini-Mental Status Test,[40,53] the Mini-Cog,[54] the Hopkins Verbal Learning Test,[55,56] and the 7-Minute Screen[57,58] are promising but need further testing in primary care populations. A new approach uses the telephone to examine cognitive function.[57,59]

A weakness of the MMSE is its varying accuracy in patients of different ages, education levels, and ethnicities.[38,60–63] The MMSE is most accurate for white people with at least a high school education.

Table 3. Accuracy of screening tests for dementia

Instrument	Sensitivity	Specificity	Positive predictive value*	Negative predictive value*
MMSE [37–44]	71% to 92%	56% to 96%	15% to 72%	95% to 99%
FAQ [37]	90%	90%	50%	99%
BIMC [37,38]	90%	65% to 90%	22% to 50%	98% to 99%
BOMC [37]	69%	90%	43%	96%
STMS [37]	81%	90%	47%	98%

Note: BIMC indicates Blessed Information Memory Concentration; BOMC, Blessed Orientation Memory Concentration; FAQ, Functional Activities Questionnaire; MMSE, Mini-Mental Status Examination; STMS, Short Test of Mental Status.

* Predictive values based on dementia prevalence of 10%.

One way of compensating for this is to change the cutpoint for an abnormal test result for different ages and education levels.[64] Whether this approach or other patient-based cognitive screening tools will be able to overcome this problem remains unclear.

The Functional Activities Questionnaire (FAQ) was the informant-based functional assessment tool that the AHCPR study examined (Table 3). Few other high quality studies have focused on functional assessments to screen for dementia. One promising screening test that warrants further study is the Informant Questionnaire on Cognitive Decline in the Elderly, which assesses change in both cognitive function as well as activities of daily living.[42]

In summary, some patient-based cognitive screening tests are available with reasonable accuracy for mild to moderate dementia, and research continues on other instruments and approaches. Although the MMSE is the most widely used and studied screening test for dementia, it requires specific adjustment for age and education. Tests of functional assessment have promise but need further study.

Because the APOE-ε4 allele is found about 3 times more frequently among people with Alzheimer's disease than among those without this condition, some groups express interest in using this test to screen for dementia.[65] Many people with Alzheimer's disease, however, do not have the APOE-ε4 allele, and many with the allele never develop dementia.[5] The value of this test in screening for dementia has yet to be demonstrated.

How Effective Are Pharmacologic Interventions for People with Mild to Moderate Dementia?

To be effective, interventions for people with dementia should ideally improve functional status to a degree discernible by caregivers or health care providers. Interpreting whether the change in an index of function in a clinical trial meets this test requires an understanding of measurement instruments for function as well as the natural history of Alzheimer's disease.

In most clinical research on Alzheimer's disease, function is measured by 1 or both of 2 scales: the Alzheimer's Disease Assessment Scale for Cognition (ADAS-Cog), a 70-point scale that measures cognitive status; and the Clinician's Interview Based Impression of Change, a scale that also includes caregiver input (CIBIC). The CIBIC includes information from both patient and caregiver interviews conducted by an experienced and independent clinician; the clinician rates the patient on a 7-point scale: 1, very much better; 4, no change; and 7, very much worse. Both the ADAS-Cog and the CIBIC scales are stable and sensitive to clinical change over time.[66]

The natural history of Alzheimer's disease is one of progressive decline; cognitive, physical, and social functions gradually deteriorate. Thus, "improvement" from an intervention for Alzheimer's disease means slowing the rate of decline. The rate of decline in Alzheimer's disease is not linear, however.[67] People with mild dementia experience an average rate of decline of 5 or fewer ADAS-Cog points (2 or fewer MMSE points) per year. Thus, for people with mild dementia, a slowing of decline by 2 to 3 ADAS-Cog points over a year could mean a delay of up to 7 months in the progress of the disease.

By contrast, those individuals with moderate dementia (ADAS-Cog >15 but < 55) experience an average decline in cognition of 7 to 11 ADAS-Cog points (2 to 4 MMSE points) annually.[67–70] Thus, for people with moderate dementia, a slowing of decline by 2 to 3 ADAS-Cog points in a year could mean a delay of 2 to 5 months in the progress of the disease. An average difference between intervention and control groups of 2 to 3 ADAS-Cog points could be attributable either to this amount of delay in disease progress for all people in the intervention group or to a longer delay in a subset of people while others have no delay. Clinically, a difference of 2 to 3 points on the ADAS-Cog[70] is equivalent, for example, to a person remembering who came to dinner the previous evening or performing familiar tasks, such as dressing.[71]

Cholinesterase Inhibitors

Four systematic reviews[72–75] and five additional RCTs[76–80] compared 1 of the 4 Food and Drug Administration-approved cholinesterase inhibitors to placebo among people with mild to moderate

Alzheimer's disease, apparently detected clinically. All 9 studies were well conducted (Table 4).

With few exceptions, all of these studies with at least 6 months of follow-up found a statistically significant difference between drug and placebo groups favoring the cholinesterase inhibitor ranging from 2.12 to 3.4 points on the ADAS-Cog scale. This difference manifests as a reduced rate of cognitive decline in people taking cholinesterase inhibitors compared with those taking placebo.

In addition to their effects on cognition, cholinesterase inhibitors also stabilized or slightly improved clinician global impression of change as measured by the CIBIC after 6 to 12 months of treatment. In many studies, the proportion of patients whose condition had stabilized was an absolute 10% to 20% higher in the cholinesterase group than in the placebo group. The evidence is mixed, however, about the effects of cholinesterase inhibitors on functional measures such as instrumental activities of daily living (ie, ability to use the telephone, mode of transportation, responsibility for medication, and ability to handle finances). In general, the studies show little or no effect on functional decline after 6 months of treatment and a small but statistically significant difference from placebo after 12 months of treatment.[81–85] The most positive study was a 12-month RCT of donepezil treatment of 431 community-dwelling people with mild to moderate Alzheimer's disease. The investigators found a median time to clinically evident decline of 6.9 months in the placebo group and 11.9 months in the donepezil group.[50, 60]

Research has found no clinically important differences between people taking cholinesterase inhibitors and those taking placebo in the development of behavioral and psychological symptoms, although not all trials measure this important health outcome. No well-conducted RCT of cholinesterase inhibitors has maintained a placebo-controlled, blinded control group for more than 12 months of treatment, and studies rarely addressed other important health outcomes such as utilization of health care services, injuries, and caregiver burden.

Ginkgo biloba, selegiline, vitamin E, and estrogen

The evidence is weak that drugs other than cholinesterase inhibitors have important benefits for people with Alzheimer's disease. Several RCTs have examined the effects of ginkgo biloba on cognitive function in people with mild to moderate dementia. Two meta-analyses of these studies, including one that examined only the 4 highest quality studies, found an approximate 3% difference in cognitive scales between ginkgo biloba and placebo groups.[16, 86]

Table 4. Efficacy of cholinesterase inhibitors in patients with Alzheimer's disease after 3 to 12 months

Drug	Patients, n	Cognitive function*	Clinician-assessed global function†	Physical function as assessed by IADLs
Tacrine [74]	1,984	1.36 to 2.78, sig.	1.18 to 2.11, sig.	Inconclusive
Donepezil [73, 76, 77, 79, 80]	1,980	2.12 to 3.01, sig.	2.04 to 2.63, sig.	Inconclusive
Rivastigmine [72, 78]	4,095	2.28 to 2.4, sig.	1.4 to 2.36, sig.	Inconclusive
Galantamine [75]	1,674	3.00 to 3.4, sig.	1.71 to 1.94, sig.	Inconclusive

Note: sig indicates statistically significant; IADL, instrumental activities & daily living.

* The mean difference between drug and placebo on the Alzheimer's Disease Assessment Scale for cognitive function, a 70-point scale.

† The odds ratio for having at least stable global function after treatment with drug in comparison with placebo as measured by the Clinician's Interview Based Impression of Change plus caregiver input scale (CIBIC).

A recent Cochrane review and meta-analysis of 15 placebo-controlled studies found that selegiline, a selective monoamine oxidase inhibitor, produced no clinically important differences in cognition, function, mood, behavior, or global clinical ratings when compared with placebo.[87] In a 2-year RCT of the effect of vitamin E in people with moderate Alzheimer's disease, investigators found that it had no effect on cognition but limited evidence that it delayed institutionalization.[88] No other well-conducted RCT has examined the effects of vitamin E. Two recent well-conducted RCTs examined estrogen therapy for women with mild to moderate dementia and found no evidence of clinical benefit.[89, 90]

Pharmacologic treatment for vascular dementia

The category of vascular dementia is heterogeneous, and the natural history of the disorder is not well understood.[91] Some people who meet criteria for vascular dementia exhibit a progressive functional decline similar to that of Alzheimer's disease.

Although antihypertensive treatment reduces the development of stroke and dementia, the evidence is limited that a similar course of treatment for people with mild to moderate vascular dementia delays progression of the disease.[92] One systematic review found that aspirin had no effect on cognitive symptoms in people with vascular dementia[93]; 1 RCT found that nimodipine (a calcium channel blocker) had no effect on the cognitive and the global symptoms of patients with vascular dementia,[92] and 1 RCT found that galantamine at least stabilized the clinician global impression of change and delayed cognitive deterioration among patients with vascular dementia as well as patients with Alzheimer's disease combined with cerebrovascular disease.[94]

Neuroleptics

Even people with mild dementia have a high prevalence of neuropsychiatric symptoms.[95] A potential benefit of early detection of dementia is that these associated problem behaviors could be recognized and treated earlier with such drugs as neuroleptics. Although RCTs have examined these agents in people with more severe dementia, no study has examined this treatment in patients with mild to moderate dementia who would be detected by screening.

Antidepressants

Many people with mild to moderate dementia are depressed.[95] Two RCTs provide evidence that antidepressants are effective for depressive symptoms among community-dwelling elderly persons with mild to moderate Alzheimer's disease. One RCT with a crossover design showed that 6 weeks of therapy with clomipramine (a tricyclic antidepressant) reduced depressive symptoms.[81] In a recent study, Lyketsos et al. found that sertraline effectively treated depression in individuals with both Alzheimer's disease and major depression.[84]

Although research demonstrates a positive effect of antidepressants on depression, it is not clear that these drugs modify the progression of dementia. No high-quality trial has examined the effect of antidepressants on health outcomes such as cognition, functional status, health-related quality of life, or clinician global impression of change.

How Effective Are Nonpharmacologic Interventions for People with Mild to Moderate Dementia and Their Caregivers?

Nonpharmacologic interventions for dementia include behavioral training, caregiver education, and supportive services. Nonpharmacologic interventions may be directed at either patients or their caregivers. Numerous studies have targeted patients with severe dementia; no study has involved people with mild to moderate dementia.

Caregiver interventions are complex and varied but usually include 1 or more of the following components: support groups, individual or family counseling, skills training, or education. Interventions targeted to caregivers are usually studied for benefit to patients as well as benefit to caregivers themselves.

One systematic review[96] and 5 well-conducted RCTs[97–102] have examined interventions directed at caregivers of people with mild to moderate

dementia (Table 5). The systematic review found no significant differences in caregiver burden between intervention and control groups and concluded that little or no evidence exists that interventions to support caregivers of people with Alzheimer's disease yield quantifiable benefit.[96] One other RCT had similar findings.[98] The other 4 studies involved multi-component interventions, and all had some positive results. Two of these focused on caregiver outcomes and found modest benefits.[101, 102] Two other studies found that intensive, comprehensive caregiver interventions enabled caregivers to maintain the affected persons at home for a substantially longer period of time (between 11 and 19 months) than those who did not receive the intervention.[103, 104]

Thus, several types of interventions targeted to caregivers showed positive impact on varied outcomes. Because of the heterogeneity of the interventions, it is difficult to determine the optimal components of these interventions.

All of these studies were conducted among clinically detected patients who required caregivers. The extent to which such interventions would be useful for family members of people with milder degrees of dementia, detected by screening, is not clear.

Does Earlier Knowledge of a Dementia Diagnosis Improve Patient and Family Planning for Future Medical Care and Safety?

Individuals identified with early dementia by screening may have the opportunity to discuss the nature of the syndrome, its prognosis, and future planning with regard to health care, safety, and finances. They may be able to formulate advance directives; choose a person to exercise power of attorney for financial and personal care decision-making; consent to participate in research; and contemplate issues such as motor vehicle driving, self-neglect, financial victimization, and housing relocation. Screening may also permit earlier and more effective treatment of co-existing conditions by improving medication adherence and avoiding drug interactions. No high-quality study has been done to verify, quantify, or refute these potential benefits.

Table 5. Summary of efficacy of caregiver interventions*

Study, year	Patients, n	Patient outcomes†	Caregiver outcomes‡	Time to nursing home placement
Hebert et al., 1994 [97] Hebert et al., 1995 [99]	45	Not significant	Not significant	Not significant
Mittelman et al., 1996 [100]	206	Not tested	Not tested	Significant
Brodaty et al., 1997 [104]	96	Not tested	Not tested	Significant
McCurry et al., 1998 [101]	36	Not significant	Significant	Not tested
Marriott et al., 2000 [102]	42	Not significant	Significant	Not tested

* Significance and non-significance were measured statistically.

† Patient outcomes included cognitive, functional, and behavioral symptoms.

‡ Included caregiver burden, depressive symptoms, and reaction to patients' behavioral problems in Hebert et al. trial; caregiver burden, depressive symptoms, sleep problems, and reaction to patients' behavioral problems in the McCurry et al. trial; and caregiver burden and depressive symptoms in Marriott et al. trial.

What Are the Adverse Effects of Screening and Early Treatment of Dementia?

The harms of dementia screening have not been systematically studied. Potential harms include risk of depression and anxiety, the time and cost of screening, and possible labeling effects. Because 50% or more of patients with a positive screening test will not meet criteria for dementia, any screening program must be linked to a source of diagnostic interviews. Although these interviews could be done by primary care physicians, relatively few nonspecialist physicians engage in such interviews as a standard part of practice. Patients and families may face delays after a positive screen before they can obtain referral for a reference standard diagnostic work-up, potentially leading to increased anxiety and worry.

Screening will also result in the detection of persons with MCI, a newly recognized condition that increases the risk of developing dementia.[105] No well-conducted RCT, however, provides information about an effective treatment for such individuals. Labeling such persons with a disease could potentially cause unnecessary anxiety.

Once a diagnosis of dementia is given, the patient will be unlikely to qualify for long-term care insurance or acceptance into a continuous care retirement community. Despite these potential hardships, however, surveys of elderly patients and caregivers of Alzheimer's patients show that most participants want to be told the diagnosis of dementia.[106, 107]

The potential harms of treatment apply primarily to drugs, both cholinesterase inhibitors and others. Common side effects experienced by people taking cholinesterase inhibitors are nausea, vomiting, weight loss, and diarrhea. In the trials of galantamine, the dropout rate attributable to adverse events in participants ranged from 2% to 15% more in the drug group than the placebo group. In the trials of rivastigmine, the adverse effect rate was from 5% to 20% higher. In trials of higher-dose (10 mg) donepezil, the adverse effect rate was about 8% higher. Tacrine has significant gastrointestinal and hepatic side effects. The odds ratio (OR) for dropout because of adverse events among people who took tacrine was 5.7 (95% confidence interval [CI], 4.1–7.9). However, in general, fewer than 20% of patients stopped taking cholinesterase inhibitors because of side effects. In RCTs of other drugs, dropout rates did not differ significantly between people who took ginkgo biloba, selegiline, or vitamin E and those who took placebo.

Discussion

The prevalence of dementia increases rapidly in the seventh and eighth decades of life; the condition affects 25% to 47% of people older than 85. Patients suffer from progressive cognitive and functional dependence, psychotic and depressive symptoms, and injuries. The burden of disease also extends to caregivers, who have high rates of emotional and financial stress and depression. Among all primary care patients older than 65 who have dementia, approximately one-half are undiagnosed.

No randomized trial has evaluated the efficacy of dementia screening in primary care. The MMSE is the best-studied brief screening tool for dementia, but it has limited specificity when the cutpoint is set for higher sensitivity, and scores must be adjusted for age and educational attainment. Other patient-based cognitive screening tests have similar characteristics. Although many of these tests take 10 minutes or less to administer, a screening program would require additional time for diagnostic interviews and patient and family counseling.

The most important problem with the evidence for screening for dementia is the uncertainty about the effectiveness of treatment for people whose disease would be detected by screening. Cholinesterase inhibitor treatment of people clinically detected with mild to moderate Alzheimer's disease provides minimal impact on functional status but a modest and consistent tendency in some people to stabilize cognition and the clinician's global impression of change. The literature makes it difficult to define clearly how many people with early dementia benefit from this treatment, and by how much. The degree to which this evidence can be extrapolated to the situation of people detected by screening is uncertain. Other pharmacologic treatments have not been adequately studied.

Limited evidence indicates that intensive, multicomponent interventions to support caregivers may delay nursing home placement for people with Alzheimer's disease, but they have demonstrated few direct benefits for either patients or caregivers. The relevance of this finding for the families of people with screening-detected dementia, who presumably do not yet have caregivers, is unclear. Additional benefits of screening, including individual and family planning and better decisions about health care interventions for other conditions, have not been studied.

Future Research Needs

Important gaps remain in our knowledge about screening for and early treatment of dementia. An RCT of screening for dementia in primary care with prospective evaluation of multiple health outcomes would provide the best evidence of benefits and harms. A trial of screening is justifiable given the high prevalence of undiagnosed dementia among primary care patients over age 65 and the efficacy of cholinesterase inhibitor treatment for clinically detected mild to moderate Alzheimer's disease. Such a trial should also monitor costs and harms and include the effects of screening and treatment on cognition, function, health care utilization, health-related quality of life, and caregiver burden.

The MMSE has been criticized for limited specificity and the need to adjust scoring for age and educational attainment. Future research should examine other promising brief screening tools that may be less education dependent, testing their positive and negative predictive value in primary care.

Although caregiver burden, increased use of health care, problem behaviors, psychiatric symptoms, and accidental injury are common in early dementia, little research to date has dealt with treatments to address these important aspects of the syndrome. The value of nonpharmacologic as well as pharmacologic interventions in the situation of early dementia merits further study. Outcome measures should be reported in order to clarify how many people benefit from these interventions and by how much. Because of the progressive nature of dementia, outcome measures that incorporate time, such as the time to decline or survival analyses, are most appropriate.

Although many uncertainties remain, the concept of detecting dementia at an early stage to allow interventions is a good one. Interventions are the only means to modify the otherwise certain decline of people with dementia. The idea of screening for dementia is worth pursuing with further research.

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Appendix

Methods

The RTI-UNC Evidence-based Practice Center (EPC), together with members of the U.S. Preventive Services Task Force (USPSTF), sought to clarify issues concerning screening for the dementia syndrome (hereafter, dementia) by performing a systematic review of the relevant scientific literature on this topic.

Analytic Framework

The systematic evidence review examined the evidence for screening for dementia. This summary of the evidence utilizes the information from the systematic evidence review, including the analytic framework. Appendix Figure 1 presents the analytic framework that we used to guide our literature search.

The analytic framework describes the logical chain that must be supported by evidence to link screening to improved health outcomes. Each arrow in the analytic framework represents a "Key Question" (Appendix Table 1); we searched systematically for evidence concerning each key question in the analytic framework.

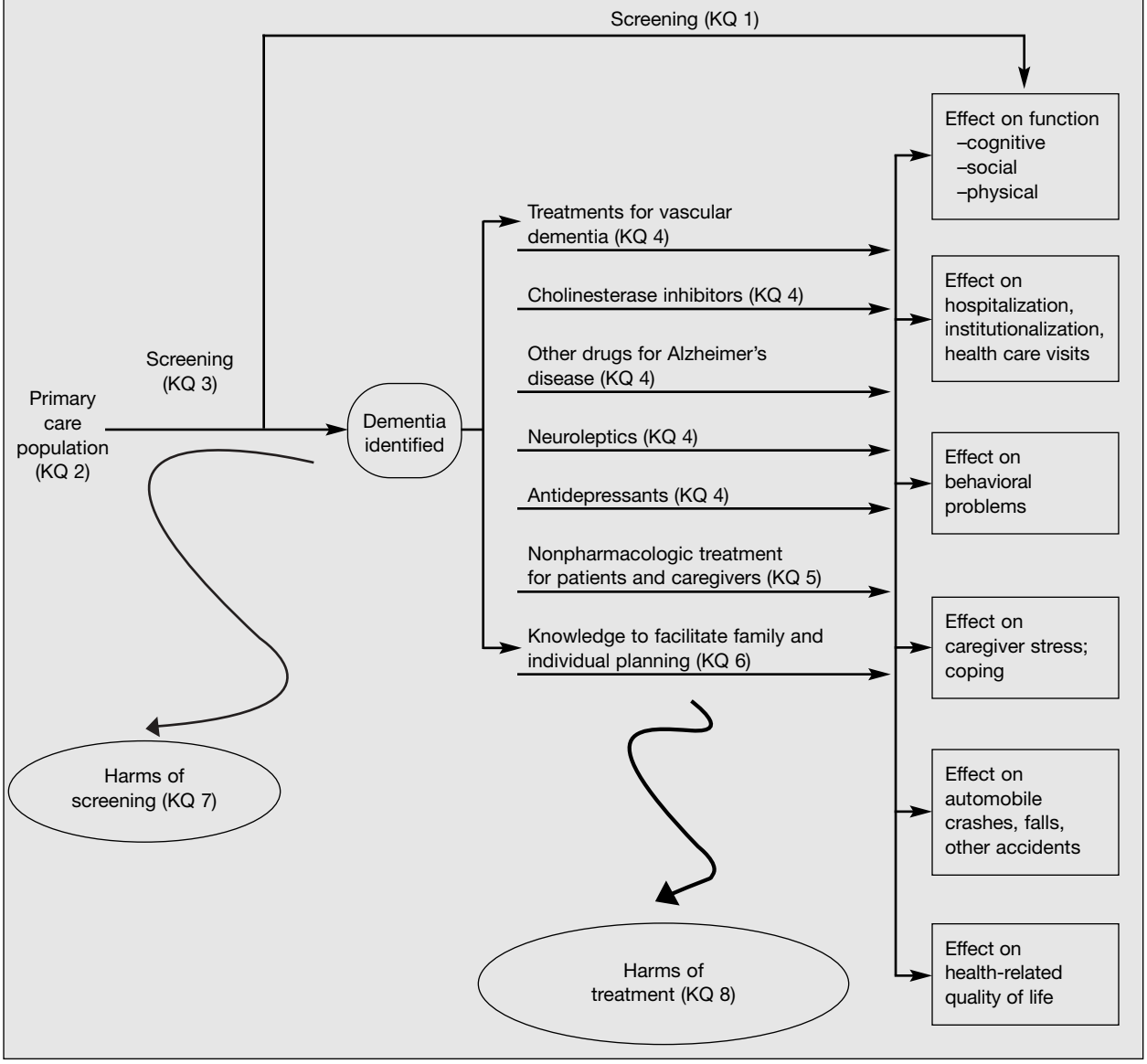
The analytic framework begins on the left side of the figure with a primary care population at risk for dementia and moves to the right. The first key question (represented by the overarching arrow) examines direct evidence that screening improves health outcomes. The health outcomes of interest are improved function (including cognitive, social, and physical); reduced hospitalizations, institutionalizations, and health care visits; fewer behavioral problems; reduced caregiver stress; fewer injuries; and improved health-related quality of life. Since we found no such overview studies, we continued to examine the indirect evidence in the following key questions, represented as linkages in the analytic framework.

KQs 2 and 3 examine the yield of screening, involving both the prevalence of undiagnosed dementia in the population and the accuracy and reliability of various screening tests.

Appendix Table 1. Key questions for screening for dementia syndrome

1. Is there direct evidence from a randomized controlled trial (RCT) of screening that screening for dementia improves health outcomes?
2. How common is undiagnosed dementia?
3. How accurate are the screening tests?
4. What is the added efficacy of initiating the pharmacologic treatments below at screening detection compared with clinical detection in improving health outcomes?
   - antihypertensives and aspirin for vascular dementia
   - cholinesterase inhibitors for Alzheimer's disease
   - other drugs (eg, ginkgo biloba, selegiline, vitamin E, estrogen) for Alzheimer's disease
   - neuroleptics
   - antidepressants
5. What is the efficacy of nonpharmacologic interventions for people with mild to moderate dementia and their caregivers?
6. Does earlier knowledge of the diagnosis of dementia improve patient and family planning for future care and safety?
7. What are the harms of screening?
8. What are the harms of treatment?

Appendix Figure 1. Analytic framework: screening for dementia



Farther to the right in the analytic framework, KQ 4 examines the efficacy of various pharmacologic treatments, including treatment with antihypertensives or aspirin to prevent the progression of vascular dementia; treatment of people with Alzheimer's disease with cholinesterase inhibitors; and treatment of people with Alzheimer's disease with other drugs, neuroleptics, or antidepressants. KQ 5 examines the effectiveness of nonpharmacologic interventions for patients or caregivers; KQ 6 involves the effect of knowledge about the diagnosis of dementia on family and individual planning.

The critical issue is the efficacy of these treatments among people who would be detected by screening. Many studies examine treatment for people with clinically detected dementia; these are useful only insofar as they allow extrapolation to the efficacy of treatment at detection by screening. Furthermore, arrows 4 through 6 (and Key Questions 4-6) actually imply that the issue of interest is the *added* efficacy of initiating treatment after screening detection as opposed to initiation after clinical detection.

At the far right in the analytic framework are the health outcomes. In the end, the indirect evidence

must allow a reasonable estimation of the magnitude of benefit in these outcomes that is attributable to screening.

At the bottom of the analytic framework is linkage and KQ 7, the issue of the harms of screening (eg, labeling), and KQ 8, concerning the harms of treatment (eg, side effects of treatment).

Eligibility Criteria for Admissible Evidence

The EPC staff and Task Force liaisons developed eligibility criteria for selecting the evidence relevant to answer the key questions (Appendix Table 2). For KQ 1, we required a well-conducted RCT of screening of adequate size and length to estimate health outcomes with reasonable accuracy. For KQs 2 and 3, we required either cross-sectional or cohort studies in which screening tests were performed on a primary care or general unselected population compared with an acceptable reference standard. For KQs 4-6, we accepted RCTs of treatments with health outcomes that provided information about the severity of participants with dementia. For KQs 7-8, we required RCTs of screened (or treated) versus non-screened (or non-treated) groups.

Literature Search Strategy, Results, and Review of Abstracts/Articles

The analytic framework and key questions guided our literature searches. We examined the critical literature described in the previous review of this topic by the USPSTF (published in 1996) (28) and used our eligibility criteria to develop search terms. We used the search terms to search MEDLINE and the Cochrane Library for English language articles that met our inclusion criteria and were published between January 1, 1994 and September 1, 2002. We also examined the bibliographies of pertinent articles and contacted experts for other references. When we found that a key question could best be answered by older literature, we also examined these studies. When we found that a systematic review used acceptable methods and that its studies met our criteria, we used the review instead of the individual studies. The search strategy and results are shown in Appendix Table 2 and Appendix Figures 1-8. All searches started with the term "dementia" and then proceeded by adding other terms as appropriate.

The first author and at least one other co-author reviewed all abstracts found through our searches to find those that met eligibility criteria. When either reviewer thought that an abstract might meet criteria, the article was copied for full review. The first author and at least one other co-author reviewed each full article. Those that met eligibility criteria after full review and discussion when necessary were abstracted. We critically appraised each study using criteria developed by the USPSTF (31). If we found a study or systematic review that met criteria but that contained a methodological flaw that invalidated its findings, we excluded it from further review. Abstracted articles or systematic reviews that met eligibility criteria and had no fatal flaws were entered into predesigned evidence tables (see Appendix B in the Systematic Evidence Review, Screening for the Dementia Syndrome, on AHRQ Web site [www.preventiveservices.ahrq.gov]).

Development of the Systematic Evidence Review and Summary of the Evidence Article

The authors presented an initial work plan including a provisional analytic framework and key questions to the entire Task Force, and also presented interim reports at subsequent meetings. The Task Force discussed and made important contributions to the review on several occasions. The two Task Force liaisons participated in every phase of the review, including conference calls to discuss critical parts of the evidence.

A draft Systematic Evidence Review (SER) was presented to the Task Force and then sent for broad peer review. The peer review included individual experts in the field, representatives of relevant professional organizations, and representatives of appropriate federal agencies. We made revisions to the evidence review as appropriate after receiving peer review comments. The Task Force reviewed all information and voted on a recommendation. We then put the SER into final form and from it developed the manuscript for journal publication.

Appendix Table 2. Dementia syndrome: eligibility criteria, search strategy, and results of searches

Key question	Inclusion criteria	Number of systematic reviews found	Number of full articles reviewed	Number of systematic reviews and articles that met criteria
All	Dementia syndrome Published 1/1/94-9/1/02 English language Human subjects, age 60+ Cochrane, MEDLINE, PsycINFO, EMBASE			
1. Direct evidence of screening	RCTs Mass screening	0	0	0
2. Prevalence of undiagnosed dementia	Systematic reviews Cross-sectional prevalence Age 60 or older in community or outpatient setting Blinded, independent evaluation for dementia syndrome diagnosed by DSM* Exclusion of subjects with prior diagnosis of dementia syndrome Valid assessment of lack of previous diagnosis	0	MEDLINE: 6 PsycINFO: 1 Total: 7	Systemic Reviews: 0 Additional Studies: 4 Total: 4
3. Accuracy of screening tests	Systematic reviews Age 60 or older in community or outpatient setting Blinded, independent evaluation for dementia syndrome diagnosed by DSM* Exclusion of subjects with prior diagnosis of dementia syndrome Data provided for true positives/negatives and false positives/negatives	Cochrane: 1 PsycINFO: 1 Other: 1 Total: 3 0	MEDLINE: 44 PsycINFO: 21 Other: 10 Total: 75	Systemic Reviews: 1 Additional Studies: 9 Total: 10
4. Efficacy of pharmacol ogic treatment	Systematic reviews RCTs Age 60 or older in community or outpatient setting Reference standard for all subjects Intervention: one of defined key questions Any of the 6 outcomes from the analytic framework	Cochrane: 12 MEDLINE: 21 EMBASE: 3 Total: 36	Cochrane: 0 MEDLINE: 232 PsycINFO: 7 EMBASE: 27 Other: 33 Total: 299	Reviews: 12 RCTs: 19 Total: 31

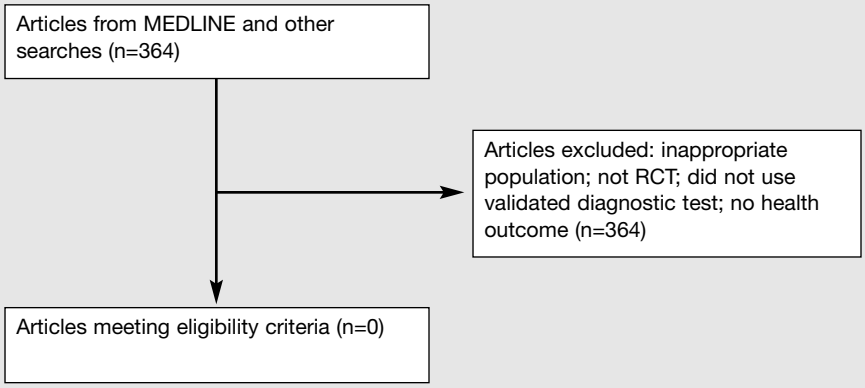
Appendix Table 2. Dementia syndrome: eligibility criteria, search strategy, and results of searches (continued)

Key question	Inclusion criteria	Number of systematic reviews found	Number of full articles reviewed	Number of systematic reviews and articles that met criteria
5. Efficacy of nonpharmacologic treatment	Systematic reviews RCTs Age 60 or older in community or outpatient setting Reference standard for all subjects Intervention: directed at patients or caregivers Health outcomes	Cochrane: 0 MEDLINE: 1 EMBASE: 0 Total: 1	Cochrane: 0 MEDLINE: 6 PsycINFO: 0 EMBASE: 0 Total: 6	Reviews: 1 RCTs: 6 Total: 7
6. Efficacy of Interventions for Planning Systematic reviews	RCTs Age 60 or older in community or outpatient setting Reference standard for all subjects Improved planning for future care	Cochrane: 0 MEDLINE: 0 EMBASE: 0 Total: 0	Cochrane: 0 MEDLINE: 0 EMBASE: 0 Total: 0	Reviews: 0 RCTs: 0 Total: 0
7. Harms of screening	Systematic reviews RCTs Age 60 or older in community or outpatient setting Reference standard for all subjects Any treatment Any possible harms of screening	Cochrane: 0 MEDLINE: 0 EMBASE: 0 Total: 0	Cochrane: 0 MEDLINE: 0 EMBASE: 0 PsycINFO: 0 Other: 0 Total: 0	Reviews: 0 RCTs: 0 Total: 0
8. Harms of treatment	Systematic reviews RCTs Age 60 or older in community or outpatient setting Reference standard for all subjects Any treatment Any possible harms of treatment	Cochrane: 12 MEDLINE: 9 EMBASE: 2 Total: 23	Cochrane: 0 MEDLINE: 228 EMBASE: 20 PsycINFO: 7 Other: 2 Total: 257	Reviews: 9 RCTs: 10 Total: 19

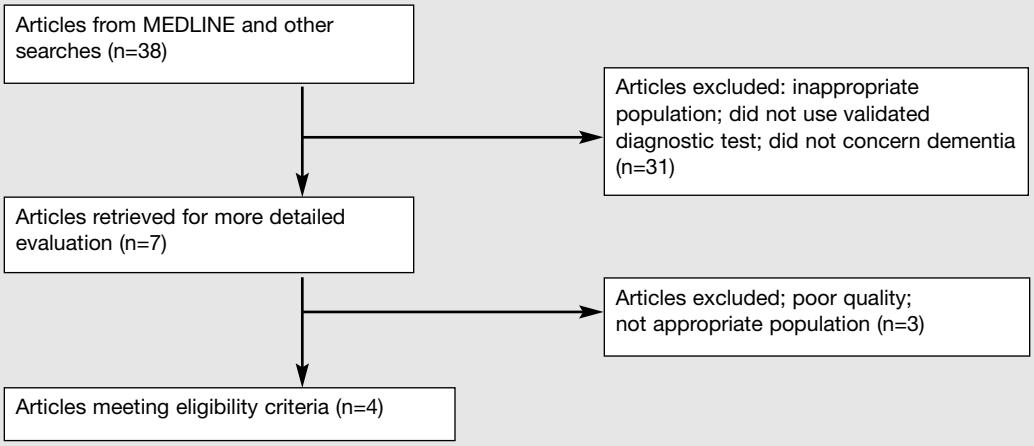
Note: RCT indicates randomized, controlled trial.

*DSM refers to *Diagnostic and Statistical Manual of Mental Disorders*, third edition; third edition, revised; or fourth edition.

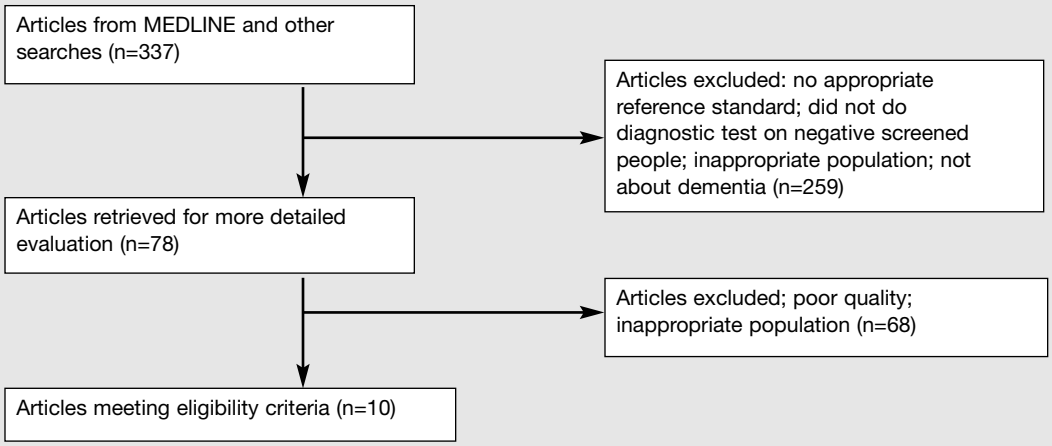
Appendix Figure 2. Selecting articles for KQ 1: direct evidence



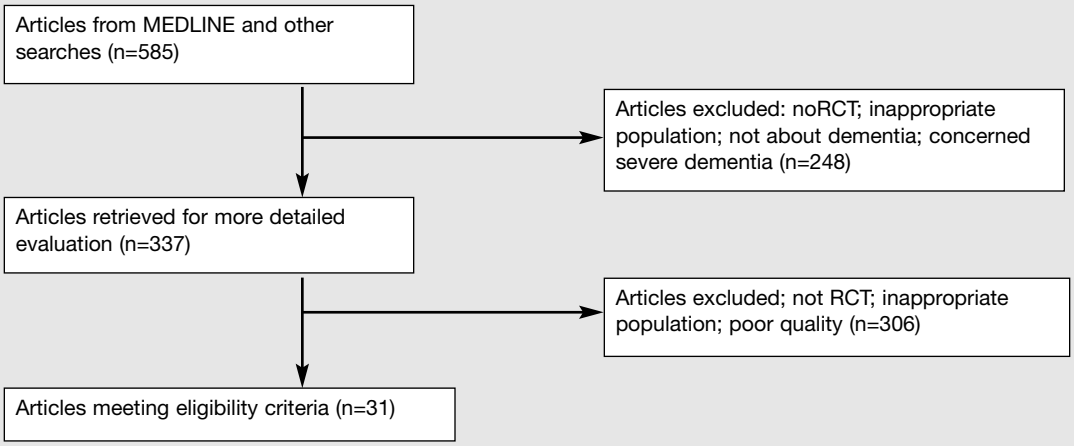
Appendix Figure 3. Selecting articles for KQ 2: prevalence of undiagnosed dementia



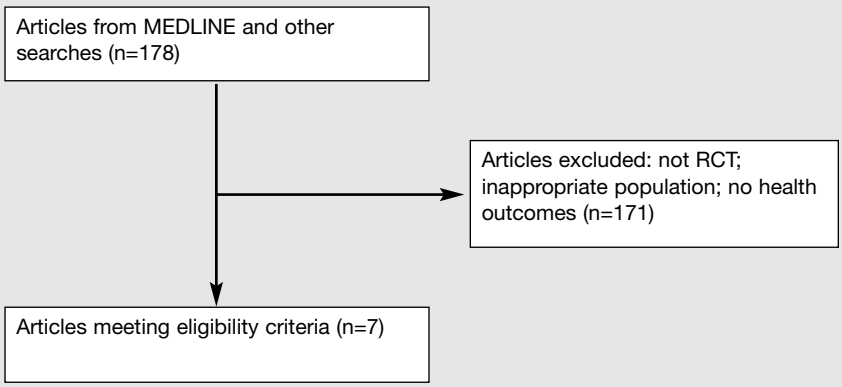
Appendix Figure 4. Selecting articles for KQ 3: accuracy of screening tests



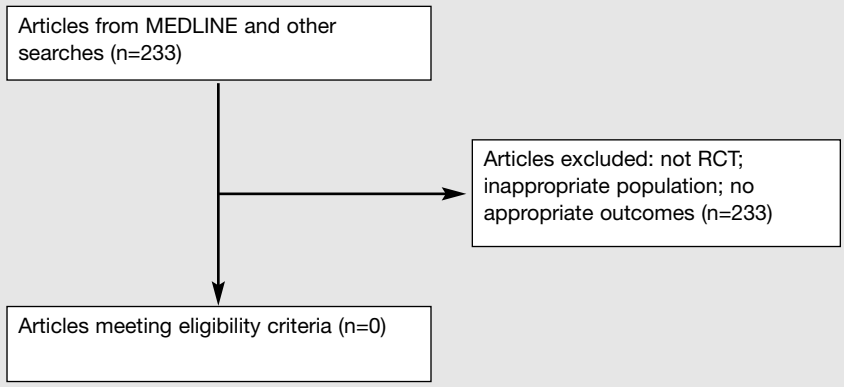
Appendix Figure 5. Selecting articles for KQ 4: efficacy of pharmacologic treatment



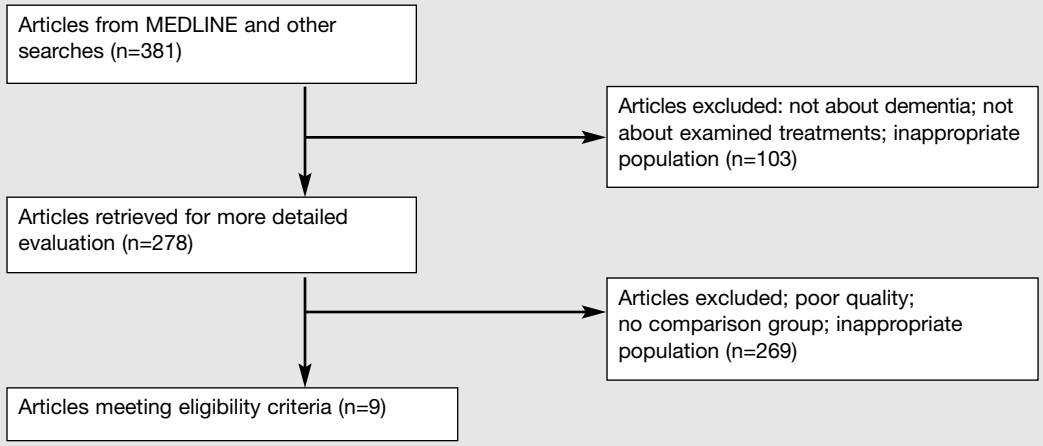
Appendix Figure 6. Selecting articles for KQ 5: efficacy of nonpharmacologic treatment



Appendix Figure 7. Selecting articles for KQ 6: interventions for planning



Appendix Figure 8. Selecting articles for KQs 7–8: harms of screening and treatment



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