HEALTHY AGING RESEARCH

Mild cognitive impairment: A comprehensive review

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Abstract

Mild cognitive impairment (MCI) represents an intermediate stage between normal cognitive changes associated with aging and dementia. Individuals with MCI have been identified as having a faster rate of progression to dementias. Risk factors for progression include greater cognitive deficits at baseline, ApoE4 carrier status, brain volume changes, cerebrospinal fluid (CSF) changes, and the presence of behavioral and psychological symptoms. Refinements in the diagnostic criteria for MCI and the identification of biomarkers to predict the progression to dementias have resulted in the appropriate diagnosis of this condition being made and the development of possible prevention and treatment strategies. Available data indicate that cognitive and physical training appears to slow the progression of the disease process. Studies of pharmacotherapeutic agents do not indicate benefit for cholinesterase inhibitors, the anti-inflammatory drug rofecoxib, or antioxidants in slowing the progression of MCI to dementias.

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Introduction

Mild Cognitive Impairment (MCI) as an official term was first used by Reisberg et al to describe individuals who were rated as a 3 on the Global Deterioration Scale (GDS) [1-4]. Subsequently, Morris et al. used the term to describe individuals with a Clinical Dementia Rating Scale (CDR) score of 0.5 [5, 6]. Petersen and colleagues further refined the concept of MCI by developing diagnostic criteria that were based on standardized neuropsychological evaluations of older adults in the community [7]. Additionally, they indicated that MCI was a distinct diagnostic entity and it was possible to differentiate these individuals from cognitively normal individuals and individuals with dementia.

At the present time, the term MCI is used to describe a state where there is a cognitive decline but it is not severe enough to meet the diagnostic criteria for a dementia [8]. The current definitions indicate that for a diagnosis of MCI to be considered, the individual should present with a decline in cognitive abilities which can be evaluated through standardized testing, but this decline in cognition cannot result in impairments in the individual's functional abilities [7-10]. Furthermore, these criteria state that the individual must not meet the diagnostic criteria for a dementia.

The National Institute on Aging-Alzheimer's Association (NIA-AA) has proposed clinical-criteria for the diagnosis of MCI [10]. This criterion includes a concern about a change in cognition when compared to the individual's previous level. The concern can be obtained from the individual, from an informant who knows the person well, or from a skilled clinician observing the person. There should be evidence of reduced performance in one or more cognitive domains that is greater than would be expected for the person's age and education. If repeated assessments are available, then a decline in performance should be evident over time. Individuals with MCI usually have mild problems in performing complex functional tasks

that they used to previously perform. They may take more time, be less efficient, and make greater errors when performing these activities at the present time of concern. However, they are generally able to independently perform functions of daily living or need only minimal assistance. The individual's cognitive changes are mild and there is no evidence of a significant impairment in social or occupational functioning.

The Diagnostic and Statistical Manual for Mental Disorders, fifth edition (DSM-5) now recognizes a pre-dementia stage of cognitive impairment termed 'mild neurocognitive disorder' (MNCD) [11]. The MNCD incorporates many features of MCI including a clinical concern raised by the individual, an informant or observations made by the clinician, cognitive impairment noted in one or more cognitive domains relative to appropriate normative data for that individual, preservation of functional independence, and no evidence for dementia. The DSM-5 criteria indicate that standardized neuropsychological testing can aid in the diagnosis of MNCD.

Epidemiology

Available evidence indicates that the prevalence of MCI ranges from 7.7% to 42.0% depending on the age groups under consideration, the country where the study was conducted, and the diagnostic criteria used to make the diagnosis [12-27] (Table 1). The data from these studies indicate that MCI commonly occurs in older adults across different cultures, races, and ethnicities.

The Mayo Clinic Study of Aging found that the prevalence of MCI increases with age [21]. Additionally this study found that MCI may be more common in men, in those who were never married, and in those individuals with APOE epsilon3epsilon4 or epsilon4epsilon4 genotype. Furthermore, MCI was noted to be less prevalent in individuals with a greater number of years of education. The Mayo Clinic Study of Aging also found that the amnestic subtype of MCI (a-MCI) was more common than the non-amnestic subtype (na-MCI) with a prevalence rate of 11.1% when compared to 4.9% for the na-MCI [21]. The most common causes for MCI in this study were

neurodegenerative disorders, especially for the a-MCI subtype [28].

In a recent review, Petersen et al, using the Mayo criteria for making diagnoses, determined the average prevalence of MCI to be 18.9%: approximately three times higher than the prevalence rate of 7% derived from major population-based studies of a-MCI [29, 30]. Additionally, using the Mayo criteria, they found that the average incidence rate was 47.9 (21.5 to 71.3) per 1000 person-years; which is more than three times greater than the average value of 15.2 (8.5 to 25.9) per 1000 person-years derived from the incidence rates of a-MCI from major population-based studies.

Table 1. Prevalence studies on MCI

Number of individuals	Age (years)	Prevalence (%)	Location	Ref.
3608	≥75	19.0	USA	12
3673	≥65	24.7	USA	13
980	75-79	19.3	Germany	14
745	≥50	14.9	India	15
2380	65-84	16.1	Italy	16
379	75-95	11.1	Sweden	17
6892	≥65	42.0	France	18
856	≥71	22.2	USA	19
2364	≥65	21.8	USA	20
1969	70-89	16.0	USA	21
1016	≥65	7.7	Italy	22
1888	≥65	16.6	Japan	23
2036	≥65	35.17	USA	24
4145	50-80	7.8	Germany	25
1673	≥65	24.1	South Korea	26
1377	65-70	20.0	Luxembourg	27

Classification

Individuals with MCI are classified into the amnestic MCI (a-MCI) or non-amnestic MCI (na-MCI) subtypes based on their performance on standardized neuropsychological tests [31]. Whereas individuals

with a-MCI present with clinically significant memory deficits, individuals with evidence of na-MCI demonstrate impairment in non-memory cognitive domains including language, executive functions, or visuospatial functions. These subtypes can be further classified into single domain or multiple domain MCIs based on the involvement of a single domain or multiple different cognitive domains [32].

Neurobiology

Available data indicate that individuals with MCI have neuropathologic changes in the brain that are intermediate between normal aging and early dementia [33, 34]. These findings suggest a transitional state that is evolving to dementia [35]. Common pathologic findings include agyrophilic grain disease, hippocampal sclerosis, and vascular lesions.

MRI studies have identified areas of atrophy in the brain of individuals with MCI including the medial temporal lobe, entorhinal cortex, hippocampus, and the posterior cingulate gyrus [36]. Additionally, amyloid-PET scans have shown increased beta-amyloid (Aβ) in several areas: the lateral frontal cortex, posterior cingulate cortex, medial and lateral parietal lobes, and the lateral temporal lobe [37, 38].

Consequences

Current data indicate that individuals with a-MCI progress to Alzheimer's disease at a rate of approximately 10% to 15% per year [7, 39-42]. These rates are significantly greater than the population incidence rates for Alzheimer's disease, which is 1% to 2% per year [32]. Risk factors for progression of MCI to dementias include the degree of cognitive impairment at evaluation, apolipoprotein E-ε4 (ApoE4) carrier status, neuropathological changes, functional changes in the brain, and changes in the cerebrospinal fluid status [29].

Individuals with more severe cognitive impairment at initial evaluation have a greater likelihood to progress to dementia and at a rate faster than those with a lesser degree of impairment [43, 44]. Additionally, individuals with a-MCI-multiple domain subtype have

a greater risk of progressing to dementia than those individuals with a-MCI-single domain subtype [32, 45]. They are also noted to have a poor survival rate compared to individuals with single domain a-MCI.

Multiple studies indicate that ApoE4 carrier status predicts the progression of MCI to dementias [46-49]. Additionally, ApoE4 carrier status is associated with a rapid progression of hippocampal atrophy as seen on an MRI scan [50].

Available data indicate that hippocampal atrophy predicts the rate of progression from a-MCI to Alzheimer's disease (AD) [51]. Additionally, studies have shown that among individuals with MCI, greater ventricular annual percent volume change, and greater whole brain annual percent volume change, increases the risk of conversion to dementia [52, 53]. Studies of individuals with MCI, using Fluorodeoxyglucose positron emission tomography (FDG-PET), show that impairments in the temporo-parietal and posterior cingulate association cortices are seen in those individuals who progress more quickly to dementia [54].

There is data that cerebrospinal fluid (CSF) concentrations of T-tau and Abeta42 at baseline yield a sensitivity of 95% and a specificity of 83% for the detection of incipient AD in individuals with MCI. Moreover, the combination of T-tau and Abeta42/P-tau181 ratio yielded a sensitivity of 95% and specificity of 87% with a hazard ratio (HR) of 19.8 [55].

The Alzheimer's Disease Neuroimaging Initiative (ADNI) study found that a combination of CSF t-tau/Aβ(1-4) ratio and MRI biomarkers, or neuropsychological tests (i.e., free recall and trail making test B (TMT-B)) showed a classification accuracy of up to 64% when applied to the prediction of MCI conversion to dementia during a 3.3-year observation interval [56]. However, several single-predictor models also showed a predictive accuracy of MCI conversion that is comparable to any multi-predictor model. The best single predictors were the right entorhinal cortex, with a prediction accuracy of 68.5%; and the TMT-B test, with a prediction accuracy of 64.6%.

Although behavioral and psychological symptoms are mainly discussed in relation to individuals with

dementias, recent evidence indicates that symptoms like depression, apathy, and anxiety are fairly common in individuals with MCI [57]. Available evidence indicates that behavioral and psychological symptoms tend to occur more commonly in individuals with MCI when compared to older adults with normal cognition: 50% vs. 25% [58]. In addition, there is emerging data that the presence of behavioral and psychological symptoms increases the rate of conversion from MCI to dementia [59-63] (Table 2).

Table 2. Baseline factors that increase the risk of conversion from MCI to dementia

1. Poor cognitive function at baseline
2. a-MCI-multiple domain subtype
3. ApoE4 carriers
4. Hippocampal atrophy
5. Greater ventricular annual percent volume change
6. Greater whole brain annual percent volume change
7. Impairment in temporo-parietal and posterior cingulate association cortices
8. Increased CSF T-tau and reduced Abeta42
9. Behavioral and psychological symptoms

Assessment

In individuals who present with complaints of cognitive difficulties, the first step is to obtain a thorough clinical history from the individual and someone who knows the person well [29, 64] (Fig.1). The next steps in the evaluation are the completion of a mental status examination and standardized cognitive testing [32]. The mental status examination and standardized cognitive testing is followed by a function assessment. Functional abilities are evaluated by means of an interview with the individual and a well-informed collateral source and the completion of standardized activities of daily living (ADL) scales. For individuals to meet the criteria for MCI, they should be independent in their functional abilities. However, slight impairment in instrumental ADL (I-ADL) is generally consistent with a diagnosis of MCI.

Functional assessment is usually followed by formal neuropsychological testing which can confirm whether these cognitive changes constitute normal aging, MCI, or a dementing illness [32]. There is no gold standard to specify which neuropsychological test battery to use, but it is important that all the major cognitive domains (i.e., executive functions, attention, language, memory and visuospatial skills) are evaluated thoroughly [29]. Reversible forms of cognitive impairment resulting from disorders like depression and/or from substance use or medication side effects should be ruled out and treated appropriately if present [11, 31]. If the individual's cognitive changes are greater than what is expected for their age but not severe enough to meet the criteria for dementia, then a diagnosis of MCI is confirmed [32] (Fig. 2).

Once a person has been diagnosed with MCI, the next task is to identify the subtype of MCI [32]. If the memory impairment is greater than what is expected for age and education, then a diagnosis of a-MCI is made [31]. If the person's memory is relatively spared but there are impairments in non-memory cognitive domains such as language, visuospatial skills, or executive functioning, then a diagnosis of na-MCI is indicated. If there is impairment of only memory domain, then a diagnosis of a-MCI-single domain is concluded [32]. In persons with a-MCI-multiple domain subtype there are impairments in memory and other cognitive domains including language, visuospatial skills, and executive functioning. Individuals with na-MCI-single domain subtype have impairment in a single non-memory domain whereas those persons with na-MCI-multiple domain subtype have impairments in multiple non-memory domains [32].

Following the determination of the subtype of MCI, the next step is to find the possible etiologies for the patient's cognitive difficulties [11, 29, 32]. The evaluations to determine the etiologies include a clinical history from the patient and informants, laboratory testing, and neuroimaging studies [29, 32]. Possible etiologies include degenerative conditions, which have a gradual onset and slower progression; or vascular events where the individual presents with an abrupt onset of symptoms. Additionally, comorbid medical conditions, such as hypothyroidism or diabetes mellitus; and psychiatric disorders, such as

depression or anxiety, can present with cognitive difficulties and should be ruled out [32].

The use of biomarkers for the identification of etiologies for MCI and for determining its progression is gaining momentum [29]. The biomarkers that have been identified by the NIA-AA workgroup as being useful include those for amyloid beta (Aβ) deposition and those of neuronal injury [10]. The biomarkers for Aβ deposition include cerebrospinal fluid concentrations of Aβ42 (CSF Aβ42) and positron emission tomography (PET) amyloid imaging. Indicators for neuronal injury are CSF tau or phosphorylated tau proteins, volumetric measures or visual rating of hippocampal or medial temporal volume/atrophy, rate of atrophy of the whole brain, fluorodeoxyglucose (FDG) PET imaging, and SPECT perfusion imaging studies.
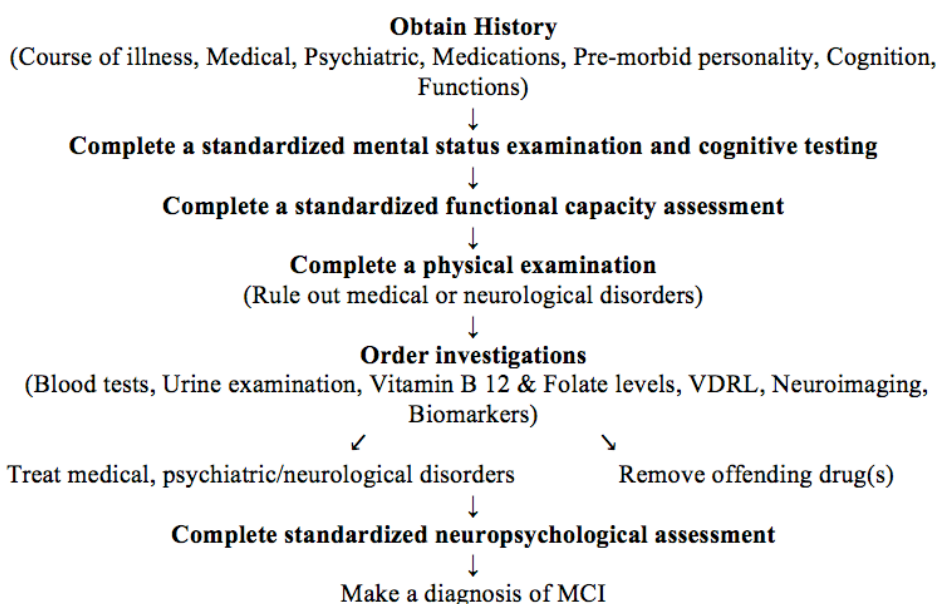

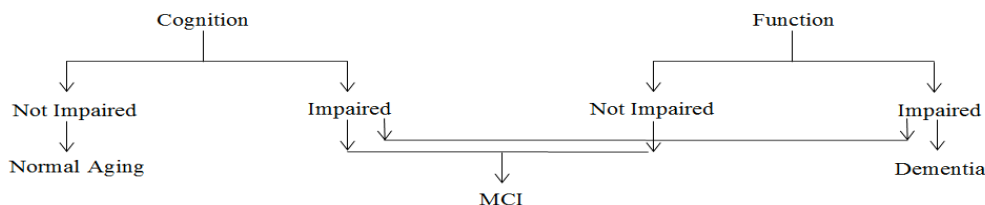**Figure 1.** Assessment of individuals with MCI

Figure 2. MCI diagnosis

Prevention

Available evidence indicates that the incidence of Alzheimer's disease is higher in individuals who do not engage in cognitively stimulating activities [7, 48, 49]. Emerging data indicate that appropriate participation in cognitively stimulating activities that involve visual and information processing like reading, doing crossword puzzles, and playing games like chess is protective against a decline in cognition and reduces the risk of Alzheimer's disease [7, 42, 51]. Nutritional studies indicate that lower consumption of fatty food, saturated fatty acids, and cholesterol is associated with reduced cognitive decline in the elderly [64].

Treatments

Non-pharmacological

Although not specific to individuals with MCI, a review by Massoud et al found that longitudinal cohort studies of healthy older adults indicate that involvement in intellectually stimulating activities was associated with decreased risk of cognitive decline and dementia [65]. Jean et al, in their systematic literature review found that addressing the efficacy of cognitive intervention programs in individuals with a-MCI resulted in a statistically significant improvement at the end of training on objective measures of memory, mood, and quality of life [66]. A randomized controlled trial (RCT) of physical activity intervention over a 24-week period found that physical activity reduces the rate of cognitive decline among older adults [67].

A meta-analysis by Li et al examining the effects of cognitive interventions in individuals with MCI showed that there was improvement in overall cognition and self-rating in addition to positive training effects in the follow-up data [68]. These individuals received small positive effects on most tasks including episodic memory, semantic memory, executive functioning, visuospatial ability, attention, processing speed and general cognition. Additionally, they received moderate benefits on language. Furthermore, the overall self-ratings, self-rated anxiety, and functional abilities showed relatively more benefit from the interventions when compared to

self-rated memory problems, quality of life, activities of daily living, and self-rated depression scores.

A systematic review of randomized controlled trials and clinical studies in healthy older adults and individuals with MCI found that cognitive training can be effective in improving various aspects of cognition including memory performance, executive functioning, processing speed, attention, fluid intelligence, and subjective cognitive performance [69]. However, the investigators found that the data on the effects of cognitive interventions on improving everyday life activities remained limited.

A recent review of the literature indicated that there is insufficient evidence to support the putative benefit on MCI from the substitution of vitamin B12, vitamin D, or testosterone when these substances are deficient. Likewise, there is insufficient evidence to support benefit from treatments for hyperhomocysteinemia, subclinical hypothyroidsm, or hormone replacement therapy after menopause on MCI [70]. However, epidemiological data suggests that a Mediterranean diet, physical activity, and moderate alcohol consumption protect against MCI while cigarette smoking promotes development of MCI.

Pharmacological

Presently, there is no Food and Drug Administration (FDA) approved medication for the treatment of MCI. However, different classes of drugs have been used in clinical trials to try and delay the progression of individuals with MCI to dementias [29]. We have only used data from systematic reviews, meta-analysis, and two controlled trials in this section to illustrate the evidence on the use of pharmacotherapeutic agents in individuals with MCI.

In a systematic review by Raschetti et al, the investigators found three trials for donepezil, two for rivastigmine and three trials for galantamine, in individuals with MCI. The duration of the trials ranged from 24 weeks to 3 years [71]. No significant differences were noted in the probability of conversion from MCI to AD or dementia between the drug-treated groups and the placebo groups. The rates of conversion ranged from 13% (2 years) to 25% (3 years) among the drug treated individuals when compared to 18% (2 years) to 28% (3 years) among

those in the placebo groups. Relative risk of conversion based on two studies was 0.85 (95% confidence interval (CI), 0.64 to 1.12) and 0.84, (95% CI, 0.57 to 1.25) respectively. However, statistically significant differences were noted for brain volume atrophy for galantamine when compared to placebo. Among the participants of these trials, at least one adverse event (AE) was noted in 88% to 96% of the drug treated group when compared to 73% to 93% of individuals in the placebo groups. Additionally, the rate of discontinuation due to AEs was higher in the drug treated group (21% to 24%) than in the placebo groups (7% to 13%).

The meta-analysis by Diniz et al found that 15.4% of the individuals assigned to the cholinesterase inhibitors-treatment group progressed to AD/dementia compared to 20.4% of the placebo group [72]. The relative risk (RR) for progression to AD/dementia in the cholinesterase inhibitors-treatment group was 0.75 (95% CI, 0.66 to 0.87, P <0.001). The individuals in the cholinesterase inhibitors-treatment group had higher all-cause dropout risk than the patients on the placebo group, RR 1.36 (95% CI, 1.24 to 1.49, P< 0.001). The RR for serious adverse events (SAE) in the cholinesterase inhibitors-treatment group was not statistically significant when compared to the placebo group (P=0.47). The subjects in the cholinesterase inhibitors-treatment group had a non-significant greater risk of death due to any cause compared to individuals in the placebo-treated group, (RR 1.04, 95% CI, 0.63 to 1.70, P=0.86).

In a double-blind study to investigate whether rofecoxib could delay the progression to AD, individuals with MCI ≥ 65 years in age were randomized to receive rofecoxib 25 mg a day or placebo for up to 4 years [73]. The primary end point was the percentage of individuals who would develop a clinical diagnosis of AD. The investigators found that the annual rate of AD was 6.4% in the rofecoxib group compared to 4.5% in the placebo group, (hazard ratio (HR) 1.46, 95% CI, 1.09 to 1.94, P=0.011). An analyses of secondary end points, including measures of cognition- the cognitive subscale of the AD Assessment Scale (ADAS-Cog)- and global function- the Clinical Dementia Rating (CDR)- did not indicate any difference between the two groups. Both groups were similar with regard to the percentages of individuals with any adverse experience, any serious

adverse experience, and those who discontinued treatment due to an adverse experience. The discontinuation rate due to drug-related adverse experiences was 8.0% in the rofecoxib group compared to 5.6% in the placebo groups.

In a trial by Petersen et al, individuals with a-MCI were randomized to receive 2000 IU of vitamin E a day, 10 mg of donepezil a day daily, or placebo for three years [74]. The primary outcome was the development of clinically possible or probable AD. Among the 769 individuals who were enrolled in the study, 212 individuals developed possible or probable AD. The overall rate of progression from a-MCI to AD was 16% per year. When compared with the placebo group, there were no significant differences noted in the probability of progression to AD in the vitamin E group, (HR 1.02, 95% CI, 0.74 to 1.41, P=0.91) or the donepezil group (HR 0.80, 95% CI, 0.57 to 1.13, P=0.42) during the three years of treatment. However, in the first 12 months of the study, the donepezil group had a reduced likelihood of progression to Alzheimer's disease when compared with the placebo group (P=0.04). Additionally, among carriers of one or more ApoE4 allele, the benefit of donepezil was evident throughout the three-year follow-up but there were no significant differences in the rate of progression to AD between the three groups. A review by Mecocci and Polidori indicated that data from available clinical trials of antioxidants use in MCI has shown that there is no clinical benefit from antioxidants in patients with MCI while tolerability may be an issue [75].

In a systematic review of RCTs evaluating the effects of any intervention for MCI on cognition, neuropsychiatric symptoms, functional and global outcomes, life quality or incident dementia, Cooper et al found a total of 41 studies that met the predetermined criteria [76]. The investigators found that the strongest evidence was that cholinesterase inhibitors did not reduce incident dementia. Additionally, cognition improved in single trials of a heterogeneous psychological group intervention over 6 months, as well as in trials of piribedil- a dopamine agonist over 3 months, and donepezil over 48 weeks. Nicotine improved attention over 6 months. Evidence was equivocal that Huannao Yicong improved cognition and social functioning.

A summary of these studies indicates that none of the pharmacotherapeutic interventions used in individuals with MCI have shown any significant benefit in delaying the progression to dementias/AD. However, brain volume reduction may be slowed by galantamine, cognition improved by piribedil, and attention improved by nicotine in individuals with MCI (Table 3).

Conclusions

Available data indicate that MCI represents an intermediate stage between normal cognitive changes associated with aging and dementia. In addition, individuals with MCI have been identified as having an accelerated rate of progression to dementias. Risk factors for progression include greater cognitive deficits at baseline, ApoE4 carrier status, brain volume and CSF changes, and the presence of behavioral and psychological symptoms. Current data indicate that cognitive and physical training appears to slow the progression of the disease process. Studies of pharmacotherapeutic agents have not indicated any benefit for cholinesterase inhibitors, the anti-inflammatory drug rofecoxib, or antioxidants in slowing the progression of MCI to dementias. Recent refinements in the diagnostic criteria for MCI and the identification of biomarkers to predict the progression to dementias enable the appropriate diagnosis of this condition to be made and for the development of appropriate prevention and treatment strategies.

Table 3. Summary of treatment studies on MCI

Intervention	Type of study	Outcome	Ref.
Intellectually stimulating activities	Review	Decreased risk of cognitive decline and dementia	65
Cognitive intervention program	Systematic literature review	Improvement in memory, mood and quality of life	66
Physical activity	RCT	Reduces the rate of cognitive decline	67
Cognitive interventions	Meta-analysis	Improvements in overall cognition and self-ratings	68
Cognitive interventions	Systematic review of RCTs	Improves cognition but not function	69
Cholinesterase inhibitors	Systematic review	No reduction in conversion rates to dementia	71
Cholinesterase inhibitors	Meta-analysis	No significant reduction in conversion rates to dementia	72
Refecoxib	RCT	No reduction in conversion rates to dementia	73
Vitamin E, donepezil or placebo	RCT	No reduction in conversion rates to dementia	74
Antioxidants	Review	No benefit	75
Any pharmacotherapeutic intervention	Systematic review of RCTs	No benefit for cholinesterase inhibitors, benefits from other agents are questionable	76

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