Modifiable Predictors of Dementia in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis

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Objective: Public health campaigns encouraging early help seeking have increased rates of mild cognitive impairment (MCI) diagnosis in Western countries, but we know little about how to treat or predict dementia outcomes in persons with the condition.

Method: The authors searched electronic databases and references for longitudinal studies reporting potentially modifiable risk factors for incident dementia after MCI. Two authors independently evaluated study quality using a checklist. Meta-analyses were conducted of three or more studies.

Results: There were 76 eligible articles. Diabetes and prediabetes increased risk of conversion from amnestic MCI to Alzheimer's dementia; risk in treated versus untreated diabetes was lower in one study. Diabetes was also associated with increased risk of conversion from any-type or non-amnestic MCI to all-cause dementia. Metabolic syndrome and prediabetes predicted all-cause dementia in people with amnestic and any-type MCI, respectively. Mediterranean diet decreased the risk of conversion to Alzheimer's dementia. The presence of neuropsychiatric symptoms or lower serum folate levels predicted conversion from any-type MCI to all-cause dementia, but less formal education did not. Depressive symptoms predicted conversion from any-type MCI to all-cause dementia in epidemiological but not clinical studies.

Conclusions: Diabetes increased the risk of conversion to dementia. Other prognostic factors that are potentially manageable are prediabetes and the metabolic syndrome, neuropsychiatric symptoms, and low dietary folate. Dietary interventions and interventions to reduce neuropsychiatric symptoms, including depression, that increase risk of conversion to dementia may decrease new incidence of dementia.

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Mild cognitive impairment (MCI) is a state between normal aging and dementia. It is defined as objective cognitive impairment relative to the person's age, with concern about the cognitive symptoms (concern of the patient, caregiver, or clinician), in a person with essentially normal functional activities who does not have dementia (1, 2). It affects 19% of people age 65 and over (3). Around 46% of people with MCI develop dementia within 3 years, compared with 3% of the age-matched population (4). People with MCI are clinically and neuropathologically heterogeneous. A subgroup of people with MCI who have progressive symptoms and particular impairment of episodic memory, termed amnestic MCI (1), or MCI due to Alzheimer's disease (2) are more likely to progress to Alzheimer's dementia.

Public health campaigns encouraging early help seeking have resulted in increasing rates of MCI diagnosis in Western countries, but we know little about how to treat or prognosticate outcomes. Neither the U.S. Food and Drug Administration (FDA) nor the U.K. National Institute for Health and Clinical Excellence recommend drug treatments, although follow-up is advised, to ensure dementia is diagnosed and care is planned early (5). People presenting with MCI want information about their risk of developing dementia and how to reduce it.

In our recent systematic review of 41 randomized controlled trials in MCI, we found no consistent evidence for the efficacy of any intervention to reduce incident dementia or cognitive decline (6). Theoretically, neuroprotection, treating vascular risk factors, or increasing cognitive reserve could be targeted at people with MCI who have a high risk of dementia. We concluded that cholinesterase inhibitors and rofecoxib are ineffective in preventing dementia. Cognition improved in single trials of 1) a heterogeneous psychological group intervention over 6 months, 2) piribedil, a dopamine agonist over 3 months, and 3) donepezil over 48 weeks. Nicotine improved attention over 6 months. There was equivocal evidence that huannao yicong, a Chinese herbal preparation, improved cognition and social functioning.

In the absence of consistent evidence of effective interventions from randomized controlled trials, observational cohort studies evaluating predictors of dementia in MCI are the best available evidence. Systematic reviews have reported that in mixed older populations, mostly without MCI, incident Alzheimer's dementia has been predicted by higher homocysteine levels, lower educational attainment, and less physical activity (7). Conflicting results have been reported for the

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association between dementia and other putative risk factors (smoking) and protective factors (mild-to-moderate alcohol consumption, dietary antioxidants, Mediterranean diet, and living with others) (8). Neuropsychiatric symptoms predict MCI in cognitively normal populations (9). These factors are possibly relevant for people with MCI, many of whom have some pathology of a dementing condition but have yet to develop clinical dementia.

In this study we synthesized evidence from longitudinal observational studies regarding modifiable risk factors that predict conversion to dementia in people with MCI.

METHOD

Search Strategy and Selection Criteria

We searched PubMed (from 1946) and Web of Knowledge (from 1900) through May 22, 2013 (updated June 5, 2014), using the terms "mild cognitive," "cognitive impairment," "benign senescent forgetfulness," "age associated cognitive decline," "age-associated memory impairment," "age-related cognitive decline" or "mild neurocognitive disorder" together with "dementia" AND "dementia incidence," "incident dementia," "incidence of dementia," "prospective," "cohort" or "longitudinal." No limits were applied for language or date of publication. We searched the references of included articles and excluded meeting abstracts.

We included longitudinal studies reporting potentially modifiable risk factors for incident dementia in people with MCI. We defined MCI as cognitive impairment identified from objective neuropsychological tests, in the absence of dementia or significant functional impairment. We included studies whether or not they specified the presence of subjective memory impairment. We report study results for people with amnestic MCI (requiring the presence of objective memory impairment), nonamnestic MCI, and any MCI type (requiring objective impairment in any cognitive domain). We specify whether predictors are given for all-cause dementia or Alzheimer's dementia. We divided studies into epidemiological studies, which identified cases of MCI from the general population or in comprehensive surveys, and clinical studies, in which people already diagnosed with MCI in clinical settings were recruited, as the rates of conversion to dementia may differ. We defined a modifiable risk factor as one potentially changeable through lifestyle or existing medical treatment.

Quality Assessment

One of us (C.C.) extracted study characteristics and findings (for the data extracted, see the tables in the data supplement accompanying the online version of this article). To assess risk of bias, two of us (C.C., A.S.) independently evaluated study quality against criteria we devised from published checklists (10):

1. The study subjects were a defined representative sample of participants assembled at a common point in the course of their disease or recruited to be representative of the general older population, with a response rate of at least 60% of eligible potential participants.
2. Participants were followed up for at least a year, with at least 70% followed up.
3. Criteria for diagnosing MCI and dementia were objective or applied in a "masked" fashion.

Disagreements were resolved by consensus. We described studies meeting all these criteria as "higher-quality" studies. We assigned grades of evidence in support of conclusions: "grade 1 evidence" was consistent evidence from higher-quality studies, "grade 2 evidence" was from a single higher-quality study or was consistent evidence from other studies, and "inconsistent evidence" was troublingly inconsistent evidence.

Data Analysis

We conducted meta-analyses (random effects models) for findings where data from three or more studies could be combined. We calculated unadjusted pooled odds ratios for dichotomous outcomes and standardized effect sizes from means and standard deviations for continuous outcomes, using Statsdirect version 2.8.0 (http://www.statsdirect.com).

RESULTS

Search Results and Validity

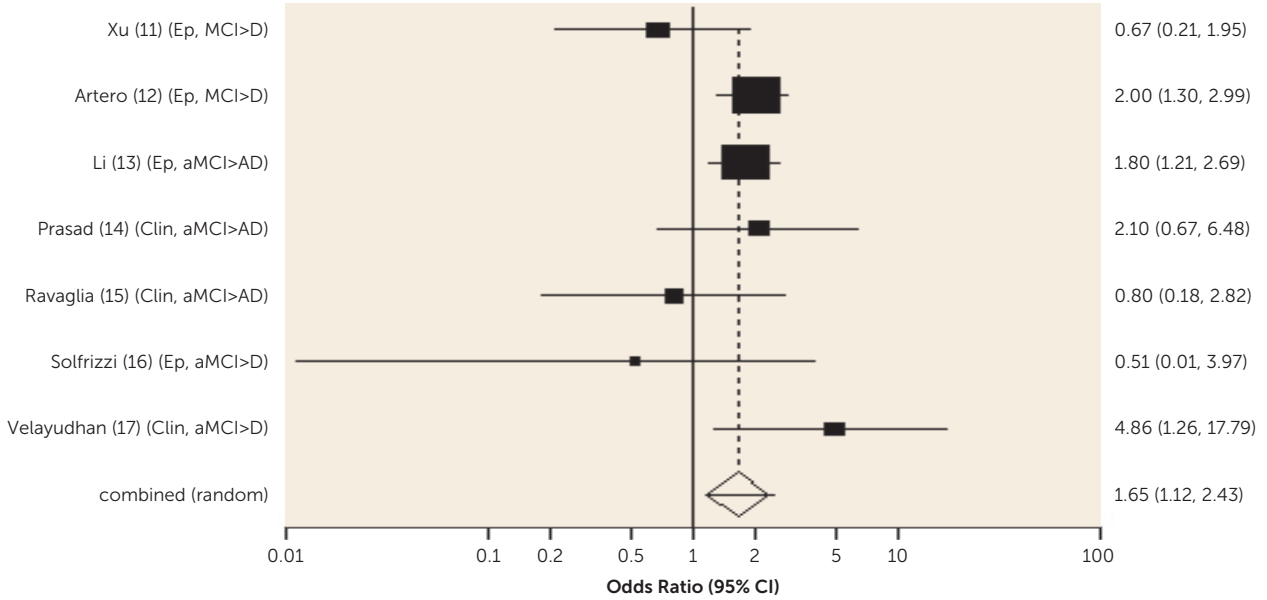
Our search strategy results are shown in Figure S1 in the data supplement accompanying the online version of this article. We included 76 articles reporting 62 studies. We report characteristics and results from the nine higher-quality studies (in 14 articles), all of which were epidemiological, and eight other epidemiological studies in Table S1 and Table S2 in the online data supplement, and 45 clinical studies (described in 58 articles) are presented online in Table S3. Thirty of the 62 studies are included in meta-analyses; other results are reported qualitatively.

Risk Factors for Cerebrovascular Disease

Diabetes. Ten studies examined diabetes, including insulin and non-insulin-dependent diabetes, with diagnoses from medical records or clinical examination and blood glucose measurement. The unadjusted pooled odds ratio for conversion to dementia in people with and without diabetes was 1.65, with a 95% confidence interval (CI) of 1.12 to 2.43, in the seven studies for which data were available (Figure 1), with the three excluded studies also showing this trend. Studies in amnestic MCI populations (reporting conversion to Alzheimer's dementia) and those with any type of MCI (reporting conversion to all-cause dementia) reported similar findings.

In large, higher-quality epidemiological (13) and clinical (18) studies, people with amnestic MCI and diabetes were more likely to progress to Alzheimer's dementia than those without diabetes, while in a third, small study a similar trend was not statistically significant (14). The higher-quality, epidemiological study reported that individuals with treated diabetes were less likely to convert to Alzheimer's dementia than those with untreated diabetes, suggesting this risk may be modifiable (13). In a further clinical study, people with

FIGURE 1. Meta-Analysis Plot for Diabetes as Predictor of MCI Conversion to Dementia[a]



[a] Meta-analysis was based on a random effects model. AD, Alzheimer's dementia; aMCI, amnestic mild cognitive impairment; Clin, clinical studies; D, any-cause dementia; Ep, epidemiological studies; MCI, mild cognitive impairment.

prediabetes or diabetes (fasting glucose >100 mg/dL) were more likely to progress from any-type MCI to Alzheimer's dementia (19).

In the only study to explore the impact of diabetes on risk of progression from nonamnestic MCI to any-cause dementia, which was a higher-quality epidemiological study, diabetes or prediabetes was a significant predictor (11). Three small and likely underpowered analyses from epidemiological studies reported the impact of diabetes on the risk of progressing from amnestic MCI to any-cause dementia (most cases of which were Alzheimer's dementia). One found that diabetes was a risk factor for progression (17), a second had a similar trend (11), and the third showed no such relationship (16).

Four studies investigated the impact of diabetes on progression from any MCI subtype to all-cause dementia. One higher-quality epidemiological study found that diabetes was a significant predictor, and prediabetes a stronger predictor, of Alzheimer's dementia and all-cause dementia, although this finding was not significant in our unadjusted analysis (Figure 1) (11). In a smaller higher-quality epidemiological study there was a trend toward diabetes being a significant predictor of conversion to any-cause dementia (hazard ratio=1.35, p=0.1) (20), while in a third epidemiological study diabetes predicted dementia (12). In a small clinical study in which only four people with diabetes developed dementia, diabetes was not predictive (15).

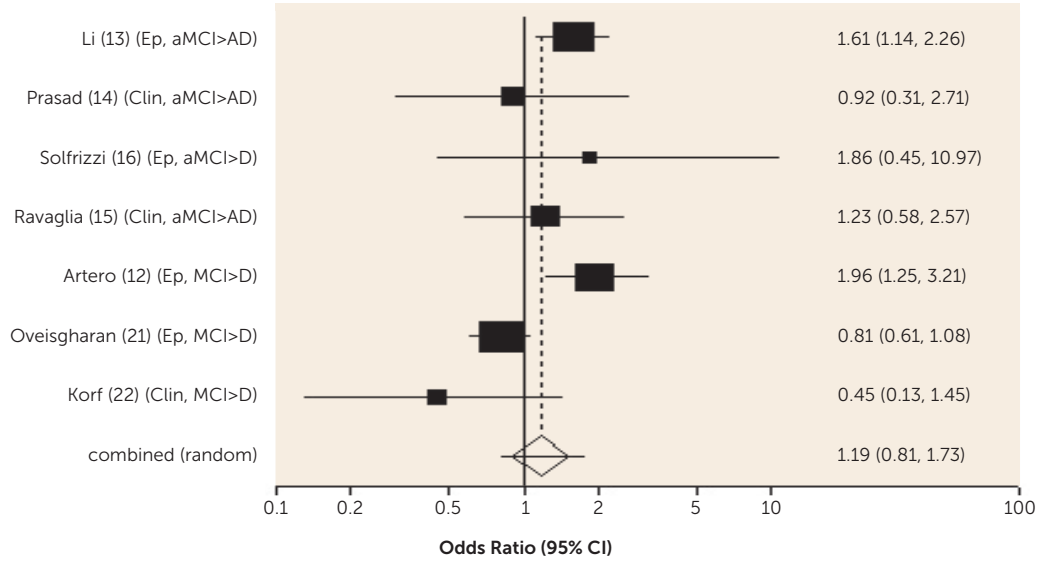
Hypertension. Eleven studies investigated current hypertension, recorded from medical records or physical examination and medication review. The unadjusted pooled odds ratio was 1.19 (95% CI, 0.81 to 1.73) for seven studies (Figure 2), with three of the studies that could not be included also showing no significant relationship (18, 20, 23) and the fourth showing that hypertension decreased conversion risk (24).

We found consistent evidence in studies of people with any-type MCI that hypertension did not predict all-cause dementia. The pooled odds ratio for four of six of these studies for which the unadjusted odds ratio was calculated (Figure 2) was 1.05 (95% CI, 0.60 to 1.85). Two of four epidemiological studies investigating this, including the only higher-quality study, found no significant relationship (20, 21). Another epidemiological study found that hypertension decreased the risk of transition to dementia from any-type MCI (24), while in the fourth study hypertension significantly increased this risk in the unadjusted analysis but not after we controlled for other factors, including stroke (12). Two clinical studies also found no such relationship (15, 22).

For conversion from amnestic MCI to Alzheimer's dementia, the evidence was less consistent. The only large, higher-quality epidemiological study to investigate conversion from amnestic MCI to Alzheimer's dementia found that hypertension did significantly predict this, while treated hypertension had a lower risk than no antihypertensive treatment (13). In three clinical studies investigating this, however, hypertension was not a significant predictor (14, 18, 23). In a small epidemiological study investigating predictors of conversion from amnestic MCI to dementia, hypertension was also not a significant predictor (16).

In addition, clinical studies showed that for each 10-mmHg decrease in systolic blood pressure or diastolic blood pressure there was a significant reduction in risk of conversion from any-type MCI to dementia (15), that systolic or diastolic blood pressure readings did not predict conversion from amnestic MCI to Alzheimer's dementia (25), and that treatment with a diuretic was associated with a lower risk of conversion from any-type MCI to Alzheimer's dementia, compared with no antihypertensive treatment (26).

FIGURE 2. Meta-Analysis Plot for Hypertension as Predictor of MCI Conversion to Dementia[a]



[a] Meta-analysis was based on a random effects model. AD, Alzheimer's dementia; aMCI, amnestic mild cognitive impairment; Clin, clinical studies; D, any-cause dementia; Ep, epidemiological studies; MCI, mild cognitive impairment.

Hypercholesterolemia. One higher-quality epidemiological study reported that hypercholesterolemia predicted conversion from amnestic MCI to Alzheimer's dementia and that people with treated versus untreated hypercholesterolemia were less likely to develop Alzheimer's dementia (13), while in a clinical study hypercholesterolemia did not predict conversion from amnestic MCI to Alzheimer's dementia (14). In two epidemiological studies, one of which was higher-quality (12, 20), hypercholesterolemia did not predict dementia in people with all-type MCI; the pooled unadjusted odds ratio from three studies (12–14) was 0.92 (95% CI, 0.50 to 1.68).

A clinical study found that people with all-type MCI who had cholesterol levels in the highest quartile (>250 mg/dL) were less likely to develop dementia than those with lower levels (15), although serum high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels did not predict conversion in the same study (27). Two other clinical studies found that serum LDL (28), HDL, and cholesterol levels (16) did not predict conversion from amnestic MCI to dementia.

Smoking. The unadjusted pooled odds ratio for a history of ever smoking was 0.45 (95% CI, 0.24 to 0.84) from three studies (15–17), but it was not significant in any study after control for age, indicating this was probably due to the competing risk of mortality. An epidemiological study reported that the mean time to all-cause dementia was shorter in people with all-type MCI who currently smoked than in those who did not (29), but those who had never smoked were at greater risk than those who had smoked for 20 pack-years or more (29, 30). This conflicting finding likely also resulted from competing mortality: smokers developed dementia younger but were more likely to die before developing dementia. Conversion from all-type MCI to any-cause dementia was not predicted by smoking status in two epidemiological studies (12, 20), one designated higher quality (20), and a clinical study after adjustment for age, gender, and education (15). There was no significant association between risk of Alzheimer's dementia in people with amnestic MCI and smoking status in a higher-quality epidemiological study (13) or a clinical study (31). Having ever smoked did not predict conversion from amnestic MCI to any dementia in adjusted analyses in two further studies (16, 17).

Alcohol. Three higher-quality epidemiological studies investigated moderate alcohol consumption. In the first, drinking alcohol, specifically wine moderately (<1 drink per day), as opposed to abstaining, predicted a lower risk of all-cause dementia in people with amnestic MCI (32). Other higher-quality studies found that daily, compared with less frequent, drinking did not predict Alzheimer's dementia in people with amnestic MCI (13) and that, compared with abstinence, neither drinking within normal limits nor harmful, risky, or addictive drinking (classified according to the World Health Organization guidelines) predicted risk of all-cause dementia in people with any type of MCI (20). While none of these studies specifically excluded heavy drinkers, few participants drank more than one drink a day in the two studies that reported overall alcohol consumption (13, 32).

Two studies, one epidemiological and one clinical, reported whether drinking any alcohol currently, as opposed to abstaining, predicted conversion from any-type MCI to dementia (12) and from amnestic MCI to Alzheimer's dementia (31). Neither study found this relationship to be significant. Finally, two clinical studies compared people with a lifetime history of heavy drinking to those without. One found that those with a history of heavy drinking were more likely, and that moderate drinkers were less likely, than abstainers to convert from any-type MCI to dementia (33). In the second, small study, which was probably underpowered, there was

a nonsignificant trend (hazard ratio=2.6, p=0.1) toward people with amnestic MCI and a history of heavy drinking being more likely to develop dementia (17).

Metabolic syndrome. Metabolic syndrome is defined as three or more of the following: abdominal obesity, elevated plasma triglycerides, low HDL cholesterol, hypertension or antihypertensive treatment, and high fasting plasma glucose. One higher-quality study showed that metabolic syndrome predicted any-cause dementia in people with amnestic MCI (34).

Summary

- There is grade 2 evidence that diabetes increases the risk of Alzheimer's dementia in people with amnestic MCI and that it increases the risk of any-cause dementia in people with any-type or nonamnestic MCI (pooled odds ratio, 1.65; 95% CI, 1.12 to 2.43) and that prediabetes predicts conversion from any-type MCI to all-cause dementia. Evidence across epidemiological and clinical studies of amnestic MCI and any-type MCI appeared consistent.
- There is grade 2 evidence that hypertension does not predict conversion from any-type MCI to all-cause dementia from epidemiological and clinical studies (pooled odds ratio=1.05; 95% CI, 0.60 to 1.85), but evidence regarding conversion from amnestic MCI to Alzheimer's dementia is inconsistent.
- There is grade 2 evidence that hypercholesterolemia is not associated with risk of conversion from any-type MCI to all-cause dementia, while evidence for the risk of Alzheimer's dementia in people with amnestic MCI is inconsistent.
- There is grade 1 evidence that smoking is not associated with risk of conversion from amnestic MCI to Alzheimer's dementia or any-type MCI to all-cause dementia when age is controlled for.
- There is grade 2 evidence that heavy alcohol use predicts conversion from any-type MCI to dementia, and there is inconsistent evidence about whether moderate alcohol use predicts risk of dementia.
- There is grade 2 evidence that the metabolic syndrome predicts a greater risk of all-cause dementia in people with amnestic MCI.

Neuropsychiatric Symptoms

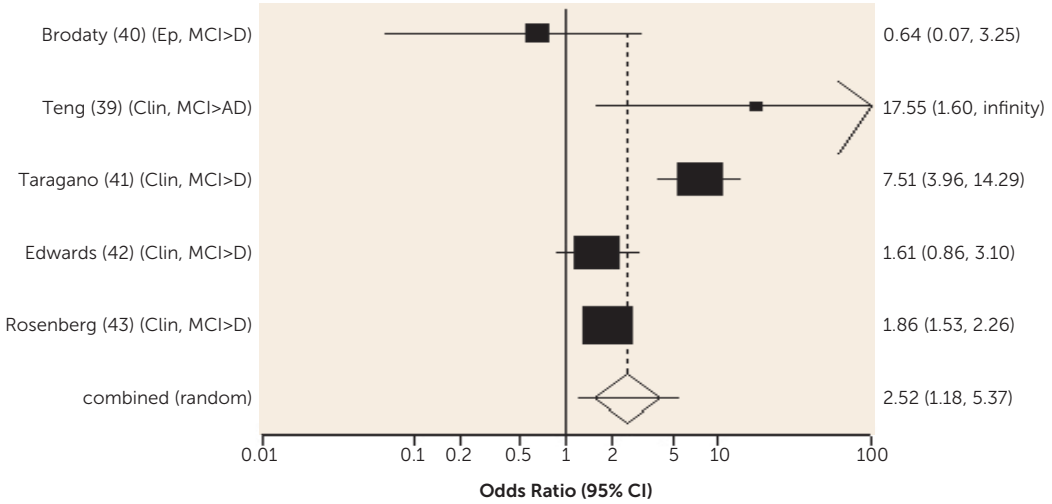
Any neuropsychiatric symptoms. Three small clinical studies found that the total score on the Neuropsychiatric Inventory was not associated with risk of conversion from any-type MCI to all-cause dementia (35, 36) or from amnestic MCI to Alzheimer's dementia (37) (pooled effect size, 0.0; 95% CI, −0.39 to 0.40). A higher-quality epidemiological study also found no association of total Neuropsychiatric Inventory score with conversion from any-type MCI to all-cause dementia, after age and education were controlled for (38), while one small additional clinical study found that it did predict conversion from any-type MCI to Alzheimer's dementia (39).

Five studies compared the proportion of participants reaching a threshold of neuropsychiatric symptoms who converted from any-type MCI to all-cause dementia (40–43) or Alzheimer's dementia (39). Four of these studies reported the proportion scoring one or more symptoms on the Neuropsychiatric Inventory, while a fifth reported the proportion scoring four or more neuropsychiatric symptoms on an unvalidated scale (42). The four clinical studies all reported a trend or significant association between having neuropsychiatric symptoms and conversion (pooled odds ratio, 3.11; 95% CI, 1.38 to 7.02) (Figure 3). One of these studies also reported that participants who scored in the middle and higher tertiles of Neuropsychiatric Inventory scores (compared with those in the lowest tertile) had a greater risk of converting from any-type MCI to all-cause dementia (43). The only epidemiological study found the reverse trend (40), so it was excluded from meta-analysis, although even when it was included the result remained significant.

Depressive symptoms. Twenty studies reported whether depressive symptoms predicted conversion, and results from 17 were included in the meta-analyses. Six clinical studies in people with amnestic MCI reported mean scores on depression rating scales, and only one (44) found a statistically significant difference between baseline scores of those who did and did not convert to any-cause dementia (28, 45) or Alzheimer's dementia (37, 44, 46, 47) (pooled standardized effect size, 0.21; 95% CI, −0.19 to 0.60) (Figure 4). Figure 5 shows the unadjusted odds ratio for having depressive symptoms from 13 studies (pooled odds ratio, 1.35; 95% CI, 0.89 to 2.06). There was heterogeneity, with the epidemiological studies that reported conversion from any-type MCI consistently finding that depressive symptoms predicted all-cause dementia, while findings from studies in amnestic MCI and clinical studies were less consistent. These analyses omitted three studies: two large, higher-quality epidemiological studies and one clinical study. The epidemiological studies found that scoring 6 or more on the Geriatric Depression Scale predicted a higher risk of dementia in people with any-type MCI; that scoring in the middle or highest tertile, compared with the lowest tertile, of the Geriatric Depression Scale also predicted a higher risk of any-cause dementia; and that scoring in the middle, compared with the lowest, tertile predicted Alzheimer's dementia in people with any-type MCI diagnosed by an experienced clinician (20, 43). The clinical study reported a nonsignificant finding (33).

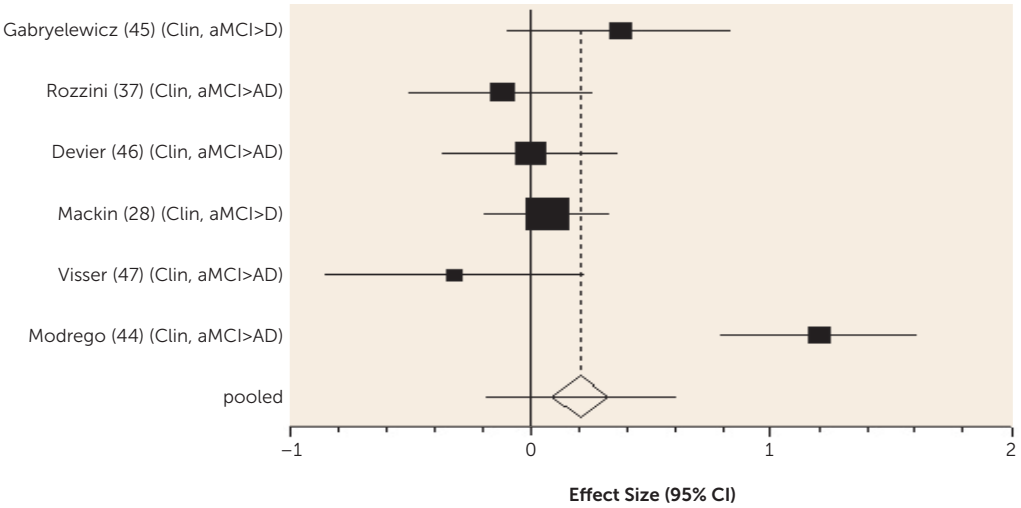
Apathy. This was examined in five clinical studies (pooled odds ratio, 1.62; 95% CI, 0.63 to 4.17) (Figure 6). In the largest study (54), reporting apathy without depressive symptoms on the relevant validated subscales of the Geriatric Depression Scale predicted conversion from amnestic MCI to Alzheimer's dementia, but apathy symptoms in the context of depressive symptoms were not a significant predictor (Figure 6). Results from four other small studies were mixed; Neuropsychiatric Inventory apathy subscale scores and apathy assessed by

FIGURE 3. Meta-Analysis Plot for Neuropsychiatric Symptoms as Predictor of MCI Conversion to Dementia[a]



[a] Meta-analysis was based on a random effects model. AD, Alzheimer's dementia; aMCI, amnestic mild cognitive impairment; Clin, clinical studies; D, any-cause dementia; Ep, epidemiological studies; MCI, mild cognitive impairment.

FIGURE 4. Meta-Analysis Plot With Effect Sizes for Depressive Symptom Score as Predictor of MCI Conversion to Dementia[a]



[a] Meta-analysis was based on a random effects model. AD, Alzheimer's dementia; aMCI, amnestic mild cognitive impairment; Clin, clinical studies; D, any-cause dementia; Ep, epidemiological studies; MCI, mild cognitive impairment.

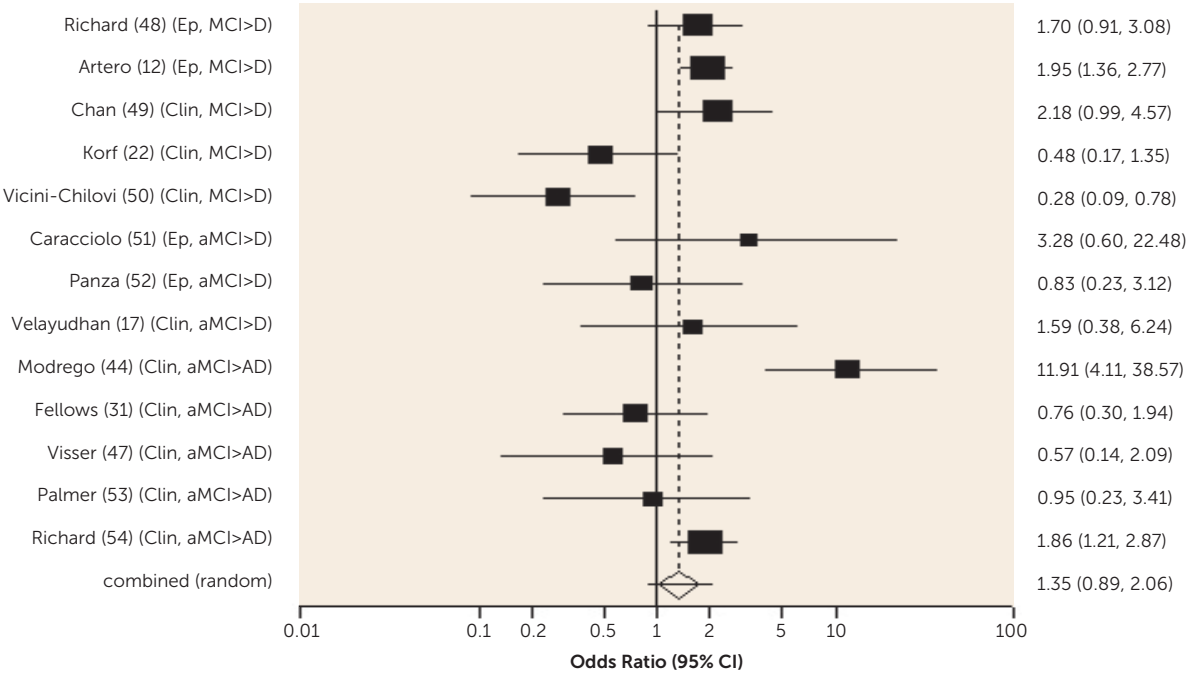
using standard criteria were associated with conversion from amnestic MCI to Alzheimer's dementia (53) with a similar but nonsignificant trend reported in a second study (55). Two small studies examined whether apathy predicted conversion from any-type MCI to all-cause dementia. Participants meeting Marin's diagnostic criteria (56) for apathy at clinical interview had a sevenfold greater odds of developing dementia (50), but having symptoms of apathy on the Chinese version of the Neuropsychiatric Inventory was not associated with developing dementia (49).

Anxiety. Three studies investigated the association of anxiety symptoms with conversion from amnestic MCI to Alzheimer's dementia. In one higher-quality epidemiological study, more anxiety on the anxiety subscale of the Comprehensive Psychopathological Rating Scale predicted Alzheimer's dementia (57). In three clinical studies, anxiety scores on validated scales did not predict conversion (37, 46, 55) (pooled odds ratio from clinical studies, −0.11; 95% CI, −0.34 to 0.11).

Summary

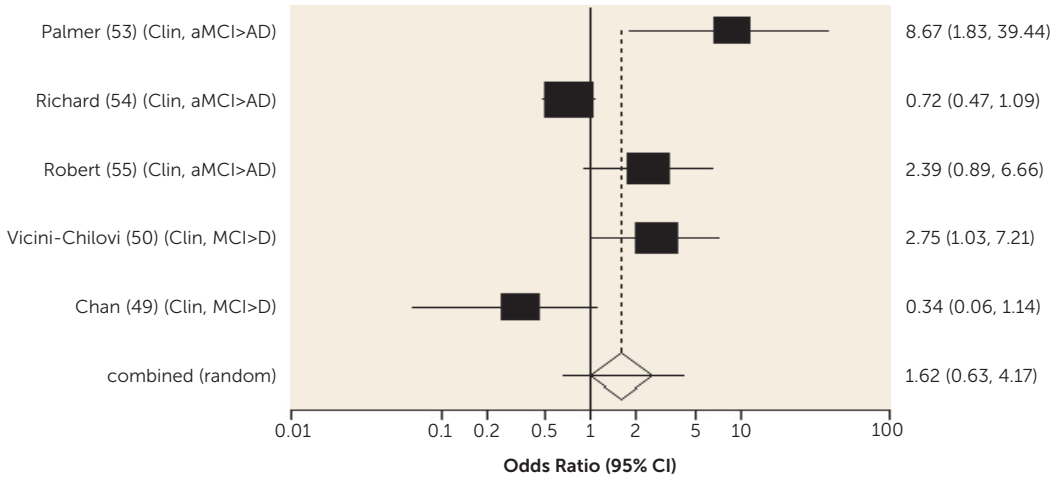
- There is grade 1 evidence that more depressive symptoms predict conversion from any-type MCI to all-cause dementia from epidemiological studies, but the evidence is inconsistent in clinical studies and about whether depressive symptoms predict conversion from amnestic MCI to Alzheimer's dementia or to any-cause dementia.
- There is grade 2 evidence from clinical studies that the presence of neuropsychiatric symptoms in people with any-type MCI, but not their overall levels of symptoms, predicts conversion to all-cause dementia.

FIGURE 5. Meta-Analysis Plot With Odds Ratios for Presence of Depressive Symptoms as Predictor of MCI Conversion to Dementia[a]



[a] Meta-analysis was based on a random effects model. AD, Alzheimer's dementia; aMCI, amnestic mild cognitive impairment; Clin, clinical studies; D, any-cause dementia; Ep, epidemiological studies; MCI, mild cognitive impairment.

FIGURE 6. Meta-Analysis Plot for Apathy as Predictor of MCI Conversion to Dementia[a]



[a] Meta-analysis was based on a random effects model. AD, Alzheimer's dementia; aMCI, amnestic mild cognitive impairment; Clin, clinical studies; D, any-cause dementia; Ep, epidemiological studies; MCI, mild cognitive impairment.

- There is inconsistent evidence about whether anxiety symptoms are associated with conversion from amnestic MCI to Alzheimer's dementia and about whether apathy predicts the risk of conversion from amnestic MCI to Alzheimer's dementia or from any-type MCI to dementia.

Dietary Factors

Mediterranean diet. In a single, higher-quality epidemiological study, adherence to a Mediterranean diet (low in meat and dairy products, high in fruits, vegetables, legumes, cereals, and fish) predicted a lower risk of conversion from amnestic MCI to Alzheimer's dementia (58).

Folate. Two studies (epidemiological and clinical) found that higher serum folate predicts a lesser risk of conversion from any-type MCI to all-cause dementia (15, 59), and a third showed a nonsignificant trend toward this (60). In one of these studies, self-reported use of folate and vitamin B12 supplements predicted a lesser risk of dementia than nonuse (but not inconsistent use), but serum B12 level did not predict dementia (59).

A higher homocysteine level, which is associated with vascular inflammation, predicted conversion from amnestic MCI to Alzheimer's dementia in a clinical study (25), and it predicted conversion from any-type MCI to all-cause dementia in one epidemiological study (61) but not in a second one (59).

A higher serum level of copper predicted conversion from amnestic MCI to Alzheimer's dementia in a single, good-quality study; it has been suggested that altered copper homeostasis is a pathogenic mechanism in Alzheimer's dementia (62).

Summary

- There is grade 2 evidence that following a Mediterranean diet decreases risk of conversion from amnestic MCI to Alzheimer's dementia.
- There is grade 2 evidence that a lower folate serum level predicts conversion from any-type MCI to all-cause dementia.
- There is inconsistent evidence about whether homocysteine serum level predicts dementia.

Education

In seven studies, years of education for people with amnestic MCI did not predict conversion to Alzheimer's dementia (14, 31, 37, 46, 47, 63, 64) or any-cause dementia (17, 22, 28) in unadjusted analyses (pooled effect size, −0.03; 95% CI, −0.16 to 0.10). Three further studies found that having more education (using dichotomized measures rather than years of education in analyses) did not predict conversion from amnestic MCI to Alzheimer's dementia (65) or any-cause dementia (16, 66). Only two studies found that education did predict conversion to Alzheimer's dementia in people with amnestic MCI (neither could be included in meta-analyses); one found that those who converted within 20 months were more likely to have had less than 10 years of schooling than those who did not (67); the second indicated that individuals with more education had an increased risk of Alzheimer's dementia (68).

Amount of education received did not predict conversion from any-type MCI to all-cause dementia in all but one of the studies that examined this relationship (22, 24, 38, 49, 59, 69–76). In one epidemiological study, less education predicted a greater risk of dementia (12). Three studies reported an association of education with conversion from any-type MCI to Alzheimer's dementia. One found that more education decreased (77) and two that it increased (36, 78) risk. Only five of the studies in people with any-type MCI (from four data sets) reported years of education in people who did and did not convert from any-type MCI to dementia, and the pooled unadjusted effect size from these studies was not significant (−0.30; 95% CI, −0.63 to 0.01) (36, 46, 49, 64, 77). Figure 7 shows the overall pooled effect size for years of education as a predictor of dementia (−0.11; 95% CI, −0.26 to 0.03) from studies of amnestic MCI and any-type MCI.

Summary

- There is grade 1 evidence from clinical and epidemiological studies that amount of education does not predict conversion from any-type MCI to all-cause dementia or from amnestic MCI to Alzheimer's dementia.

Other Significant Predictors

More physical activity (79), low body mass index (15), or atrial fibrillation (80) predicted conversion from any-type MCI to all-cause dementia in clinical studies. "Antidementia drugs" reduced the risk of conversion from any-type MCI to all-cause dementia in a clinical study (81) but not in a higher-quality epidemiological study (20). Estrogen replacement therapy predicted a shorter time to conversion from any-type MCI to all-cause dementia (a mean of 1.3 years [SD=0.5] versus a mean of 2.8 in the whole sample; p=0.003), but not a greater likelihood of dementia (29).

When age was controlled for, anticholinergic drug use predicted conversion from any-type MCI to all-cause dementia among women but not men in an epidemiological study (12).

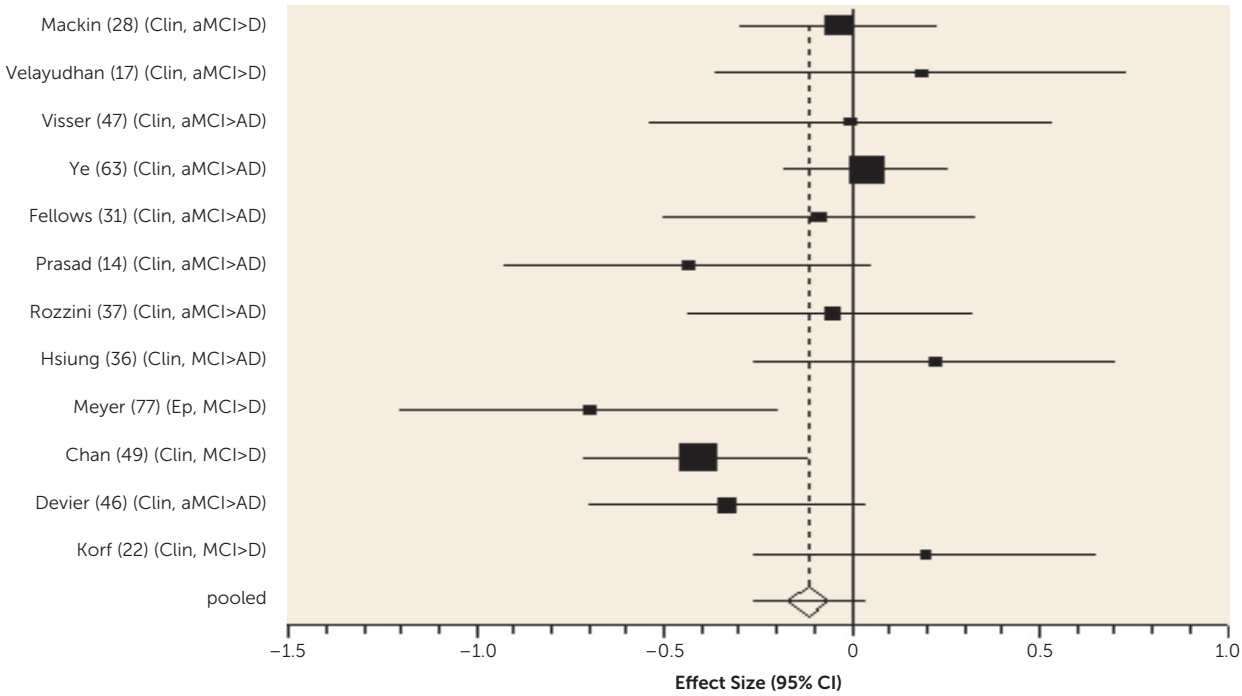
DISCUSSION

Diabetes was associated with an increased risk of conversion from amnestic MCI to Alzheimer's dementia and from any-type MCI to all-cause dementia, and the risk was lower in one study for those receiving treatment for diabetes. Metabolic syndrome and prediabetes predicted all-cause dementia in people with amnestic MCI and any-type MCI, respectively, in one study. Older people without MCI who have diabetes are known to be at increased risk of Alzheimer's, vascular, and all-cause dementia (10). Our review shows that diabetes remains an important predictor of dementia in people with MCI and suggests it may be helpful to ensure this is detected and treated.

Diabetes and the metabolic syndrome are associated with atherosclerosis and brain infarcts, and glucose-mediated toxicity causes microvascular abnormalities. Hyperinsulinemia, a symptom of type II diabetes or result of insulin replacement, has been associated with cognitive decline and Alzheimer's dementia (82), probably mediated by vascular disease and possible direct brain effects. Cerebral insulin receptors are abundant in the hippocampus and the cortex, and insulin inhibits beta amyloid degradation, the main product of the Alzheimer's dementia process (82). Evidence of impaired insulin receptor activation in the brains of people with Alzheimer's dementia (83) has led to suggestions that Alzheimer's dementia may be "an insulin resistant brain state" (10).

Similar mechanisms could explain the finding from one of the reviewed studies that adherence to a Mediterranean diet predicts a lower risk of amnestic MCI conversion to Alzheimer's dementia. Mediterranean diet adherence is associated with fewer vascular risk factors and with reduced plasma glucose and serum insulin levels, insulin resistance, and markers of oxidative stress and inflammation (58). Higher folate levels predicted a lesser risk of conversion from any-type MCI to all-cause dementia, and they have also been shown to predict lower medial temporal lobe atrophy (59). These findings are similar to those in populations not selected for presence of mild cognitive impairment: that lowering saturated fat intake (84), increasing vegetable consumption (85), and Mediterranean diet adherence (86) appear to protect against dementia. We did not find that hypercholesterolemia or hypertension

FIGURE 7. Meta-Analysis Plot for Years of Education as Predictor of MCI Conversion to Dementia[a]



[a] Meta-analysis was based on a random effects model. AD, Alzheimer's dementia; aMCI, amnestic mild cognitive impairment; Clin, clinical studies; D, any-cause dementia; Ep, epidemiological studies; MCI, mild cognitive impairment.

predicted conversion to dementia. In a systematic review of predictors of dementia in non-MCI populations, hypertension decreased risk of vascular dementia (87), but relatively few of the studies we reviewed reported vascular dementia as an outcome. Midlife, but not late-life, total cholesterol levels have been shown to predict Alzheimer's dementia and any-cause dementia (88) in general populations, so for hypercholesterolemia and perhaps other vascular risk factors, intervention may be effective only if delivered before the onset of MCI.

A third to three-quarters of people with MCI have neuropsychiatric symptoms, most commonly depression, anxiety, apathy, and irritability (89). Neuropsychiatric symptoms predicted conversion from any-type MCI to all-cause dementia. Neuropsychiatric symptoms may be etiologic for dementia, for example through neuroendocrine axis activation, or they may interact synergistically with a biological factor, such as genetic predisposition. Either of these putative relationships suggests that treating neuropsychiatric symptoms could theoretically delay dementia. Alternatively, neuropsychiatric symptoms may indicate more severe pathology (90). Greater anterior cingulum pathology in people with MCI and Alzheimer's dementia has been associated with more irritability, agitation, dysphoria, apathy, and nighttime behavioral disturbances (91). Serotonergic dysfunction is probably of particular relevance to neuropsychiatric symptoms, including depression and aggression (92), suggesting that serotonergic drugs might theoretically treat neuropsychiatric symptoms and reduce risk of progression; in one preliminary study fluoxetine improved cognition in people with MCI compared with placebo after 8 weeks (93). We found that depressive symptoms predicted conversion from any-type MCI to all-cause dementia in epidemiological studies, but evidence from clinical studies was inconsistent. This might be due to lack of power in the clinical studies. In non-MCI populations, affective disorders appear to be a risk factor for dementia, as well as a prodromal symptom, in clinical and epidemiological studies (94).

We found higher-quality evidence that amount of formal education received does not predict dementia in MCI. According to the cognitive reserve model, education delays clinical manifestations of brain pathology, so people with more education have worse neuropathology for any level of cognitive impairment (95), and in the older general population, low education does predict dementia (7). While the onset of MCI may be delayed in those with more education, our review indicates that progression to dementia is not delayed once MCI is diagnosed, consistent with cognitive reserve theory.

Limitations

We gave higher priority to positive findings but also described null results reported in more than one higher-quality study. Lack of evidence of prediction is not evidence of lack of prediction. Many factors found to be associated with dementia risk in populations in whom most did not have MCI, for example physical activity and omega-3 fatty acids (7), were not studied in the included articles or were insufficiently studied, e.g., homocysteine (7). We excluded studies where the outcome was progression of cognitive impairment rather than incident dementia. There is known to be a degree of inaccuracy in dementia diagnoses in clinical and epidemiological studies, which may have compromised the validity of some study findings.

Almost all studies included any cause dementia or Alzheimer's dementia as outcomes, rather than other subtypes; few reported vascular dementia as an outcome, and predictors, especially vascular risk factors, are likely to differ from those of degenerative dementias such as Alzheimer's dementia.

Future Research

Associations in naturalistic longitudinal studies do not imply causation; we do not know whether preventing or treating diabetes, neuropsychiatric symptoms, and depression, where possible, or Mediterranean diet adherence might reduce the risk of Alzheimer's dementia or all-cause dementia. In many people with MCI, vascular risk factors and dietary habits are longstanding, and pathology may not be reversible. In the absence of effective MCI treatments, however, our findings suggest that managing components of the metabolic syndrome, dietary interventions, and social interventions are logical targets for future trials.

Methodological challenges for MCI trials include defining the study population. Only two-thirds of people with MCI progress to dementia in their lifetime (96), limiting the power of secondary prevention studies that recruit MCI populations. The heterogeneity and instability of the MCI diagnosis militate against finding positive results in MCI trials. Availability of biomarkers may enable future trials to recruit participants according to disease process rather than clinical deficits; in a recent study, a panel of 10 proteins predicted progression from MCI to Alzheimer's dementia with an accuracy of 87% (97). Biomarkers may also allow participants to be recruited when the pathological process is less advanced and treatments more effective. Incident dementia is often the primary outcome as dementia prevention is a clear goal, but Schneider has suggested it is a problematic endpoint because many participants would be on the cusp of dementia and dementia onset is influenced by numerous biological and environmental factors (98).

Conclusions

Further good-quality randomized controlled trials are necessary to identify evidence-based dementia prevention strategies, and the increasing availability of biomarkers will assist in recruitment of more homogenous populations with high likelihood of dementia conversion, improving trial efficiency. In our recent review of randomized controlled trials (6), we found no consistent evidence that any intervention prevents conversion from MCI to dementia. The findings of this systematic review suggest that managing diabetes and components of the metabolic syndrome and dietary interventions are logical targets for future trials.

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