ARTICLE

Modifiable predictors of dementia in Mild Cognitive Impairment: a systematic review and meta-analysis

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Abstract
Objectives: 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 prognosticate dementia outcomes in persons with MCI.
Method: We 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. We meta-analysed findings from three or more studies.
Results: We identified 76 eligible papers. Diabetes and prediabetes increased risk of conversion from amnestic MCI (aMCI) to Alzheimer's Dementia (AD); 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 pre-diabetes predicted all cause dementia in people with aMCI and any type MCI respectively. Mediterranean diet decreased risk of conversion from aMCI to AD. 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 dementia in epidemiological, but not clinical studies.
Conclusions: Diabetes increased the risk of conversion to dementia. Other prognostic factors that are potentially manageable are pre-diabetes and the metabolic syndrome, neuropsychiatric symptoms and low dietary folate. Dietary interventions and interventions to reduce neuropsychiatric symptoms including depression, which increase conversion risk to dementia, may decrease incident dementia.

Key Words: dementia, mild cognitive impairment, longitudinal studies

Introduction

Mild cognitive impairment (MCI) is a state between normal aging and dementia. It is defined as objective cognitive impairment for age, with concern about cognitive symptoms (whether concern of the patient, carer or clinician) in a person with essentially normal functional activities, who does not have dementia[1;2]. It affects 19% of people aged 65 and over[3]. Around 46% of people with MCI develop dementia within 3 years compared to 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 (aMCI)[1] or MCI due to Alzheimer's disease[2], are more likely to progress to AD.

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 UK National Institute for Health and Clinical Excellence (NICE) recommend drug treatments, although follow-up is advised, to ensure dementia is diagnosed and care 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 Randomised Controlled Trials (RCT) 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: a heterogeneous psychological group intervention over 6 months; piribedil, a dopamine agonist over 3 months; and 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 RCT evidence of effective interventions, 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 AD has been predicted by higher homocysteine levels, lower educational attainment, and decreased physical activity[14]. Conflicting results have been reported for the 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)[16]. Neuropsychiatric symptoms predict MCI in cognitively normal populations[15]. 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.

Objectives

To synthesise evidence from longitudinal, observational studies regarding modifiable risk factors that predict conversion to dementia in people with MCI.

Methods

Search strategy and selection criteria

We searched PubMed (1946-) and Web of Knowledge (1900-) through 22 May 2013 (updated 5 June 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 time published. We searched references of included papers. We 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 aMCI (requiring presence of objective memory impairment), non-aMCI, any MCI type (requiring objective impairment in any cognitive domain), and also predictors of all cause dementia, Alzheimer's dementia, or other dementias separately. 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

CC extracted study characteristics and findings (see Tables for data extracted). To assess risk of bias, two authors (CC, AS) independently evaluated study quality against criteria devised by the authors, derived from published checklists[17]:

1. 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. Participant follow-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 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 standardised effect sizes from means and standard deviations for continuous outcomes using Statsdirect version 2.8.0.

Results

Search results

Figure 1 shows our search strategy results. We included 76 papers reporting 62 studies.

Validity

We report characteristics and results from the 9 higher quality studies, all epidemiological (in 14 papers) and 8 other epidemiological studies in Tables 1 and 2; and 45 clinical studies (described in 58 papers) in Table 3. 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 (OR) for conversion to dementia in people with and without diabetes was 1.65 (95% CI 1.12 to 2.43) for the 7/10 studies (Figure 2a) for which data was available, with the three excluded studies also showing this trend. Studies in aMCI populations (reporting conversion to AD) and any type MCI populations (reporting conversion to all cause dementia) reported similar findings.

In large, higher quality epidemiological[18] and clinical[19] studies, people with aMCI and diabetes were more likely to progress to AD than those without diabetes, while in a third, small study a similar trend was not statistically significant[20]. The higher quality, epidemiological study, reported those with treated diabetes were less likely to convert to AD than those with untreated diabetes, suggesting this risk may be modifiable[18]. In a further clinical study, people with prediabetes or diabetes (fasting glucose >100 mg/dL) were more likely to progress from any type MCI to AD[21].

In the only study to explore the impact of diabetes on risk of progression from non-amnestic MCI to any cause dementia, a higher quality epidemiological study, diabetes or prediabetes was a significant predictor[22]. Three small and likely underpowered epidemiological studies reported the impact of diabetes on the risk of progressing from aMCI to any cause dementia (of whom most had AD). One found that diabetes was a risk factor for progression[23], a second a similar trend[22] and the third no such relationship[24].

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 AD[22]. In a smaller higher quality epidemiological study there was a trend towards diabetes being a significant predictor of conversion to any cause dementia (HR 1.35, p=0.1)[25], while in a third epidemiological study diabetes predicted dementia[26]. In a small clinical study in which only four people with diabetes developed dementia, diabetes did not predict dementia[27].

Hypertension: Eleven studies investigated current hypertension, recorded from medical records or physical examination and medication review. The unadjusted pooled OR was 1.19 (95% CI 0.81 to 1.73) for the 7/11 studies (Figure 2b), with three of the studies that could not be included also showing no significant relationship[19;25;28] and a fourth that hypertension decreased conversion risk[29].

We found consistent evidence that in studies of people with any type MCI, hypertension predicted all cause dementia. Pooled OR for 4/6 of these studies for which unadjusted OR was calculated (Figure 2b) was 1.05 (0.60 to 1.85). Two of four epidemiological studies investigating this, including the only higher quality study, found no significant relationship[25;26;30]. Another epidemiological study found that hypertension decreased the risk of transition to dementia from any type MCI[29], while in the fourth study hypertension significantly increased this risk on unadjusted analysis, but not when controlled for factors including stroke[26]. Two clinical studies also found no such relationship[27;31] .

For conversion from aMCI to AD, the evidence was less consistent. The only large, higher quality epidemiological study to investigate conversion from aMCI to AD found that hypertension did significantly predict this, while treated hypertension had lower risk than no antihypertensive treatment[18]. In three clinical studies investigating this however, hypertension was not a significant predictor[19;20;28]. In a small epidemiological study investigating predictors of conversion from aMCI to dementia, hypertension was also not a significant predictor[24].

In addition, clinical studies reported that for each 10mmHg decrease in systolic blood pressure or diastolic blood pressure there was a significant reduction in risk of conversion from any type MCI to dementia[27]; and that systolic or diastolic blood pressure readings did not predict conversion from aMCI to AD[32] and treatment with a diuretic was associated with a lower risk of conversion from any type MCI to AD, compared with no antihypertensive treatment[33].

Hypercholesterolemia: One higher quality epidemiological study reported that hypercholesterolemia predicted conversion from aMCI to AD, and that those with treated versus untreated hypercholesterolemia were less likely to develop AD[18], while in a clinical study hypercholesterolaemia did not predict conversion from aMCI to AD[20]. In two epidemiological studies, one of which was higher quality[25;26], hypercholesterolemia did not predict dementia in people with all type MCI [pooled unadjusted OR from 3 studies[18;20;26] 0.92 (0.50 to 1.68)].

A clinical study found that people with all type MCI who had cholesterol levels in the highest quartile (>250mg/dL) were less likely to develop dementia than those with lower levels[27], although serum HDL and LDL levels did not predict conversion in the same study[34]. Two other clinical studies found that serum LDL[35], HDL and cholesterol levels[24] did not predict conversion from aMCI to dementia.

Smoking: The unadjusted pooled OR for a history of ever smoking was 0.45 (95% CI 0.24 to 0.84) from three studies[23;24;27], but was not significant in any study after controlling 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[36]; but those who had never smoked were at greater risk than those who had smoked for 20 pack years or more[36;37]. This conflicting finding likely also resulted from competing mortality: smokers developed dementia sooner, 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[25;26], one higher quality[25], and a clinical study after adjusting for age, gender and education[27]. There was no significant association between risk of AD in people with aMCI and smoking status in

a higher quality epidemiological[18] or a clinical study[38]. Ever smoking did not predict conversion from aMCI to any dementia in two further studies[23;24].

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 aMCI[39]. Other highest quality studies found that daily, compared to less frequent drinking did not predict AD in people with aMCI[18], and that compared to abstinence, neither drinking within normal limits, nor harmful, risky or addictive drinking (classified using World Health organisation guidelines) predicted risk of all cause dementia in people with any type MCI[25]. 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[18;39].

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[26] and from aMCI to AD[38]. Neither study found this relationship was 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, and moderate drinkers less likely than abstainers to convert from any type MCI to dementia[40]. In the second, small study that was probably underpowered, there was a non-significant trend (HR 2.6, p=0.1) towards people with aMCI who had a history of heavy drinking being more likely to develop dementia[23].

Metabolic syndrome (3+ of: abdominal obesity; elevated plasma triglycerides; low HDL cholesterol; hypertension or anti-hypertensive treatment; and high fasting plasma glucose): one highest quality study showed that metabolic syndrome predicted any cause dementia in people with aMCI[41].

Summary

- There is *grade 2* evidence that diabetes increases the risk of AD in people with aMCI or any cause dementia in people with any type or non-amnestic MCI [pooled OR 1.65 (95% CI 1.12 to 2.43), and that prediabetes predicted conversion from any type MCI to all cause dementia. Evidence across epidemiological and clinical, and aMCI and any type MCI studies 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 OR 1.05 (0.6 to 1.85)], but evidence regarding conversion from aMCI to AD was 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 AD in people with aMCI was inconsistent.
- There is *grade 1* evidence that smoking is not associated with risk of conversion from aMCI to AD, or any type MCI to all cause dementia after controlling for age.
- There is *grade 2* evidence that heavy alcohol use predicts conversion from any type MCI to dementia, and *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 aMCI.

Neuropsychiatric symptoms (NPS)

Any NPS: Three small clinical studies found NPI total scores were not associated with risk of conversion from any type MCI to all cause dementia[42;43] or aMCI to AD[44] (pooled effect size 0.0, -0.39 to 0.40). A higher quality epidemiological study also found no association of total Neuropsychiatric Inventory (NPI) score with conversion from any type MCI to all cause dementia, after controlling for age and education[45], while one small additional clinical study found that it did predict conversion from any type MCI to AD[46].

Five studies compared the proportion of participants reaching a threshold of NPS who converted from any type MCI to all cause dementia[47-50] or AD[46]. Four studies reported the proportion scoring one or more on the NPI[47], while a fifth reported the proportion scoring four or more NPS on an unvalidated scale[49]. The four clinical studies all reported a trend or significant association between having NPS and conversion (pooled OR 3.11, 1.38 to 7.02). One of these studies also reported that those who scored in the middle and higher tertile of NPI scores (compared to the lowest) had a greater risk of converting from any type MCI to all cause dementia[50]. The only epidemiological study found the reverse trend[47] so was excluded from meta-analysis, although even when included the result remained significant.

Depressive symptoms: Twenty studies reported whether depressive symptoms predicted conversion, and results from 17 were included in meta-analyses. Six clinical studies in people with aMCI, reported mean scores on depression rating scales, and only one[51] found a statistically significant difference between baseline scores of those who did and did not convert to dementia[35;52] or AD[44;51;53;54] [pooled standardised effect size 0.21, -0.19 to 0.60; see Figure 2d]. Figure 2c shows unadjusted OR for having depressive symptoms from 13 studies [pooled OR 1.35, 0.89 to 2.06]. There was heterogeneity, with the epidemiological studies reporting conversion from any type MCI consistently finding depressive symptoms predicted all cause dementia, while findings from studies in aMCI and clinical study findings were less consistent. These analyses omitted three studies; two large, higher quality epidemiological and clinical studies respectively which found scoring six or more on the GDS predicted a *higher* risk of dementia in people with any type MCI; and that scoring in the middle or highest compared with the lowest tertile of the GDS also predicted a *higher* risk of any cause dementia, and scoring in the middle compared to the lowest predicted AD in people with any type MCI diagnosis made by an experienced clinician[25;50]; and a clinical study that reported a non-significant finding[42].

Apathy: This was examined in five clinical studies [pooled OR 1.62, 0.63 to 4.17; Figure 2f].In the largest study, reporting apathy symptoms but not depressive symptoms on the relevant validated Geriatric Depression Score (GDS)-15 subscales[55] predicted conversion from aMCI to AD, but apathy symptoms alone were not a significant predictor (Figure 2e). Results from four other small studies were mixed; NPI apathy subscale scores and apathy assessed using standard criteria was associated with conversion from aMCI to AD[56] with a similar but non-significant trend reported in a second study[57]. Two small studies examined whether apathy predicted conversion from any type MCI to all cause dementia. Participants meeting Marin's diagnostic criteria for apathy at clinical interview had a seven-fold greater odds of developing dementia[58], but having symptoms of apathy on the Chinese NPI[59] was not associated with developing dementia.

Anxiety: Three studies investigated the association of anxiety symptoms with conversion from aMCI to AD. In one higher quality epidemiological study, more anxiety on the CPRS subscale predicted AD[60]. In three clinical studies, anxiety scores on validated scales did not predict conversion[57;44;53] [pooled OR from clinical studies -0.11, -0.34 to 0.11].

Summary

- There is *grade 1* evidence that more depressive symptoms predicted conversion from any type MCI to all cause dementia from epidemiological studies, but *inconsistent* evidence from clinical studies and about whether they predicted conversion from aMCI to AD or dementia.
- There is *grade 2* evidence from clinical studies that people with any type MCI reporting NPS, but not the overall levels of symptoms, predicted conversion to all cause dementia.
- There is *inconsistent* evidence about whether anxiety symptoms are associated with conversion from aMCI to AD, or whether apathy predicted the risk of conversion from aMCI to AD, or any type MCI to dementia.

Dietary factors

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 aMCI to AD[61].

Folate: Two studies (epidemiological and clinical) have found that higher serum folate predicts a lesser risk of conversion from any type MCI to all cause dementia[27;62;62] and a third showed a non-significant trend towards this[63]. In the former study, self-reported folate and vitamin B12 supplement use predicted a lesser risk of dementia compared with non-users, but not inconsistent users but serum B12 levels did not predict dementia.

Higher homocysteine levels (associated with vascular inflammation) predicted conversion from aMCI to AD in a clinical study[32], and conversion from any type MCI to all cause dementia in one[64], but not a second epidemiological study[62].

Higher serum levels of copper predicted conversion from aMCI to AD in a single, good quality study; it has been suggested that altered copper homeostasis is a pathogenic mechanism in AD[65].

Summary

- There is *grade 2* evidence that following a Mediterranean diet decreases risk of conversion from aMCI to AD.
- There is *grade 2* evidence that lower folate serum levels predict conversion from any type MCI to all cause dementia.
- There is *inconsistent* evidence about whether homocysteine serum levels predict dementia.

Education

In seven studies, years of education for people with aMCI did not predict conversion to AD[20;31;38;44;53;66;67] or any cause dementia[23;35;54] on unadjusted analyses [pooled effect size -

0.03, -0.16 to 0.10]. Three further studies found that education did not predict conversion from aMCI to AD[68;69] or any cause dementia[24;70]. Only two studies found that education did predict conversion to AD in people with aMCI (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[69]; the second that those with more education had an increased risk of AD[71].

Amount of education received did not predict conversion from any type MCI to all cause dementia in 15 of 16 studies to examine this[29;31;45;59;62;72-80]. In one epidemiological study, less education predicted a greater risk of dementia[26]. Two studies reported the association of education with conversion from any type MCI to AD. One found that more education decreased[43;43] and one that it increased[81] risk. Only five of the studies in people with any type MCI (from four datasets) 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, -0.63 to 0.01)[43;53;59;67;80]. Figure 2g shows the overall pooled OR for years of education as a predictor of dementia (-0.11, -0.26 to 0.03) from aMCI and any type MCI studies.

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 aMCI to AD.

Other significant predictors

More physical activity[82], low Body Mass Index (BMI)[27] or atrial fibrillation[83] 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[84], but not in a higher quality epidemiological study[25]. Oestrogen replacement therapy predicted shorter time to conversion from any type MCI to all cause dementia (mean 1.3 +/-0.5 years, versus mean of 2.8 in whole sample; p=0.0029), but not greater likelihood of dementia[36].

Anticholinergic drug use predicted conversion from any type MCI to all cause dementia after controlling for age among women, but not men in an epidemiological study[26].

Discussion

Diabetes and prediabetes were associated with an increased risk of conversion from aMCI to AD and the risk was lower in one study for those receiving treatment for diabetes. Metabolic syndrome and pre-diabetes predicted all cause dementia in people with aMCI and any type MCI respectively in one study. Older people without MCI who have diabetes are known to be at increased risk of AD, vascular and all cause dementia[17]. Our review shows that diabetes remains an important predictor of AD in people with aMCI 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 AD[85], 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 AD process[85]. Evidence of impaired insulin receptor activation in AD brains[86] has led to suggestions AD may be "an insulin resistant brain state"[17].

Similar mechanisms could explain the finding from one of the reviewed studies that adherence to a Mediterranean diet predicts a lower risk of aMCI to AD conversion. Mediterranean diet adherence is associated with fewer vascular risk factors, and reduced plasma glucose and serum insulin levels, insulin resistance and markers of oxidative stress and inflammation[61]. 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[62]. These findings are similar to those in populations not selected for presence of mild cognitive impairment, that lowering saturated fat intake[87], increasing vegetable consumption[88] and Mediterranean diet adherence[89] appear to protect against dementia. We did not find that hypercholesterolaemia or hypertension predicted conversion to dementia. In a systematic review of predictors of dementia in non-MCI population, hypertension decreased risk of vascular dementia[90], but relatively few of the studies reported vascular dementia as an outcome. Midlife, but not late life total cholesterol levels have been shown to predict AD and any cause dementia[91] in general populations, so for hypercholesterolaemia and perhaps other vascular risk factors, intervention may only be effective if delivered before the onset of MCI.

A third to three-quarters of people with MCI have NPS; most commonly depression, anxiety, apathy and irritability[92]. NPS predicted conversion from any type MCI to all cause dementia. NPS may be etiologic for dementia, for example through neuroendocrine axis activation; or interact synergistically with a biological factor, such as genetic predisposition; either of these putative relationships suggest that treating NPS could theoretically delay dementia. Alternatively, NPS may indicate more severe pathology[93]. Greater anterior cingulum pathology in people with MCI and AD has been associated with more irritability, agitation, dysphoria, apathy, and night time behavioral disturbances[94]. Serotonergic dysfunction is probably of particular relevance to NPS, including depression and aggression[95], suggesting serotonergic drugs might theoretically treat NPS and reduce risk of progression; in one preliminary study fluoxetine improved cognition in people with MCI compared with placebo after 8 weeks[96]. 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[97].

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,[98] and in the older general population, low education does predict dementia[14]. 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 prioritised 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[14] were not studied in included papers, or insufficiently studied, e.g. homocysteine[14]. 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 AD 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 AD.

Future Research

Associations in naturalistic, longitudinal studies do not imply causation; we do not know whether preventing or treating diabetes, NPS and depression, where possible, or Mediterranean diet adherence, might reduce the risk of AD or 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 study population. Only two- thirds of people with MCI progress to dementia in their lifetime[99], 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 AD with an accuracy of 87%[100]. 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[101].

Conclusions

Further good quality RCTs 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 RCTs we found no consistent evidence for any intervention preventing conversion from MCI to dementia. The findings of this systematic review suggest that managing diabetes, components of the metabolic syndrome and dietary interventions are logical targets for future trials.

Authorship and Disclosure statements

Dr Claudia Cooper

Conceived, conducted systematic review, extracted data, rated study quality, wrote manuscript first draft and acts as guarantor. Dr Cooper reports no disclosures.

Dr Andrew Sommerlad

Rated study quality, revised manuscript critically for important intellectual content and approved final version. Dr Sommerlad reports no disclosures.

Professor Constantine Lyketsos
Revised manuscript critically for important intellectual content and approved final version. Professor Lyketsos reports the following disclosures: Grant support (research or CME): NIMH, NIA, Associated Jewish Federation of Baltimore, Weinberg Foundation, Forest, Glaxo-Smith-Kline, Eisai, Pfizer, Astra-Zeneca, Lilly, Ortho-McNeil, Bristol-Myers, Novartis, National Football League, Elan, Functional Neuromodulation; Consultant/Advisor: Astra-Zeneca, Glaxo-Smith Kline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, Pfizer, Genentech, Elan, NFL Players Association, NFL Benefits Office, Avanir, Zinfandel, BMS, Abvie, Janssen, Orion. Honorarium or travel support: Pfizer, Forest, Glaxo-Smith Kline, Health Monitor

Professor Gill Livingston

Revised manuscript critically for important intellectual content and approved final version. Professor Livingston reports no disclosures.

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Figure 1: PRISMA Flow Diagram

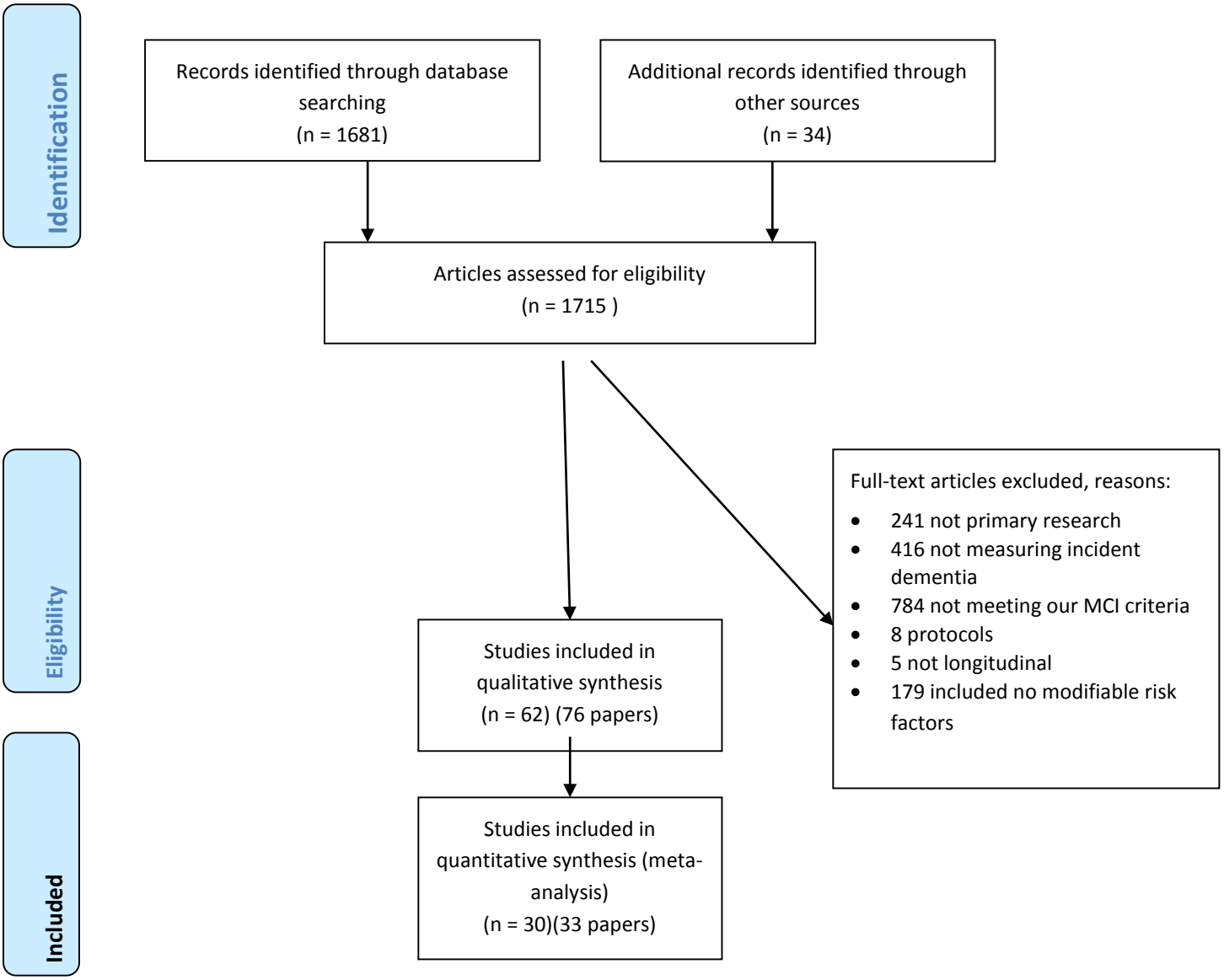


Figure 2: Meta-analysis plots [random effects]

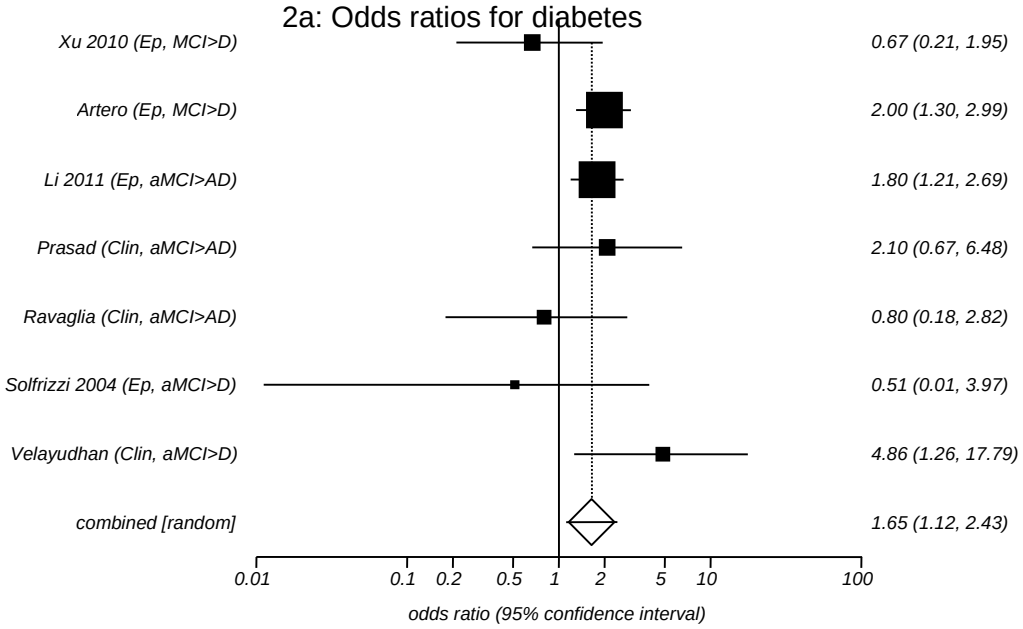


Figure 2b: Odds ratios for current hypertension

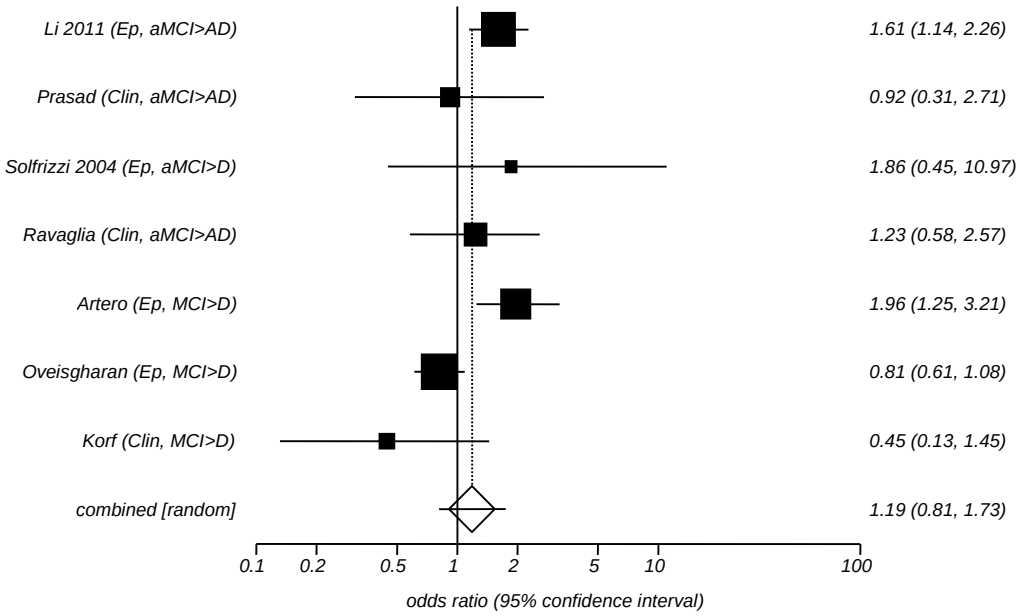


Figure 2c Effect size , depressive symptoms

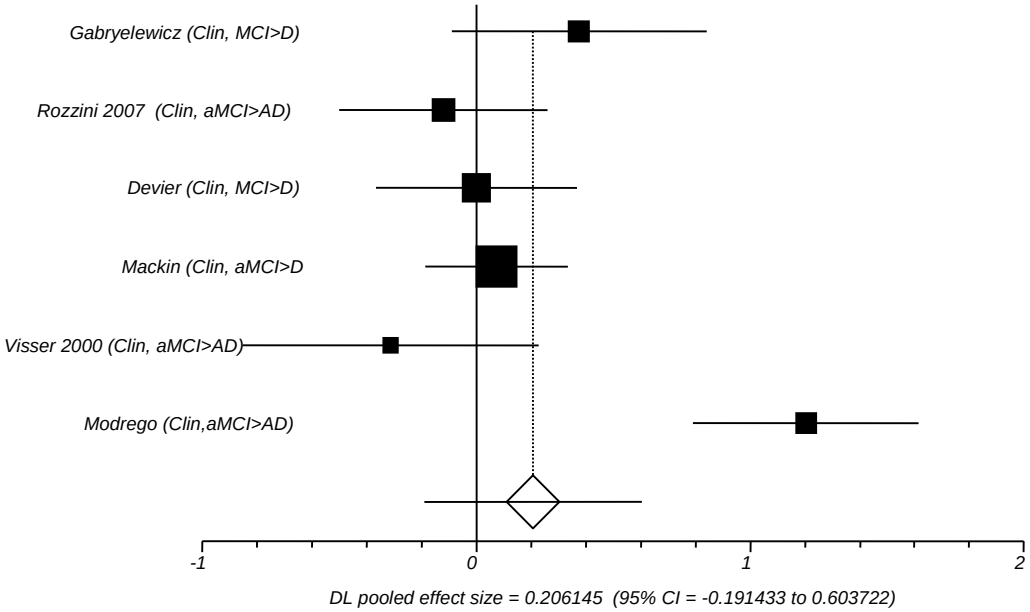


Figure 2d: Odds ratios for depressive symptoms

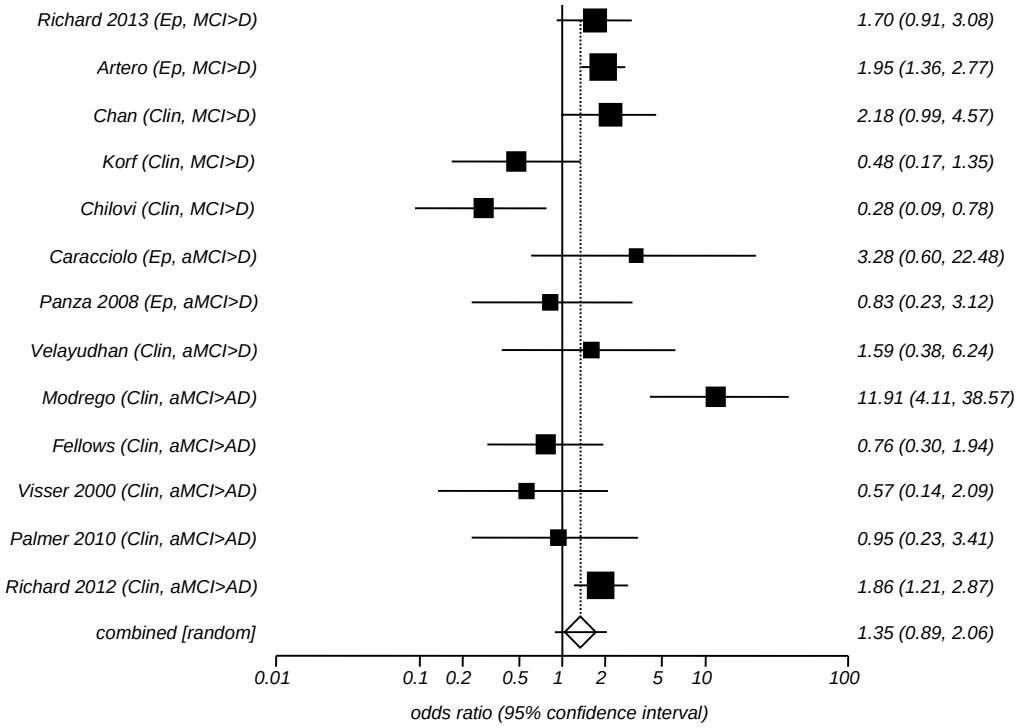


Figure 2e Apathy Odds ratio

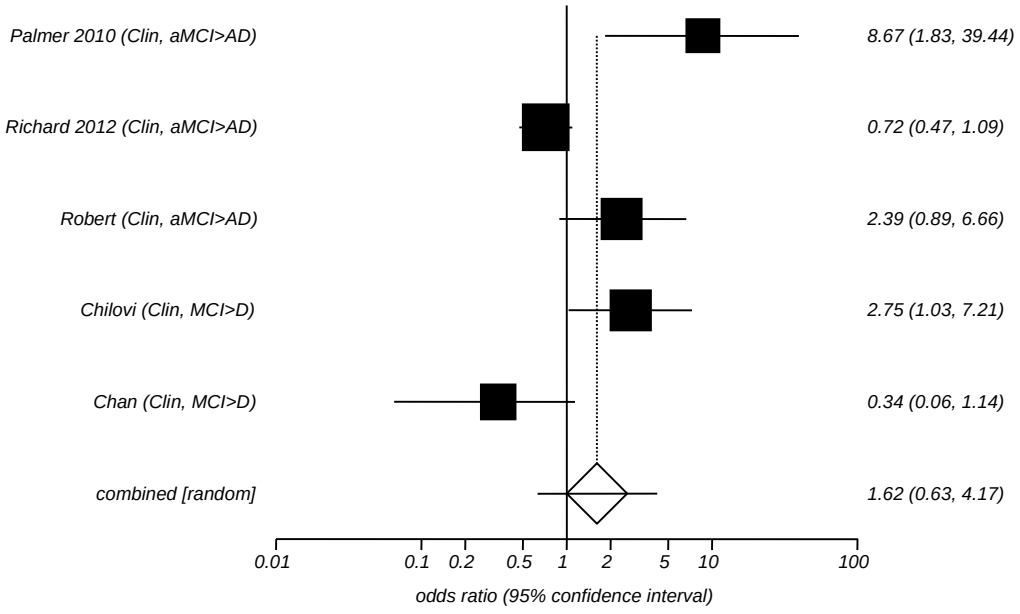


Figure 2f: Odds ratio, Neuropsychiatric symptoms

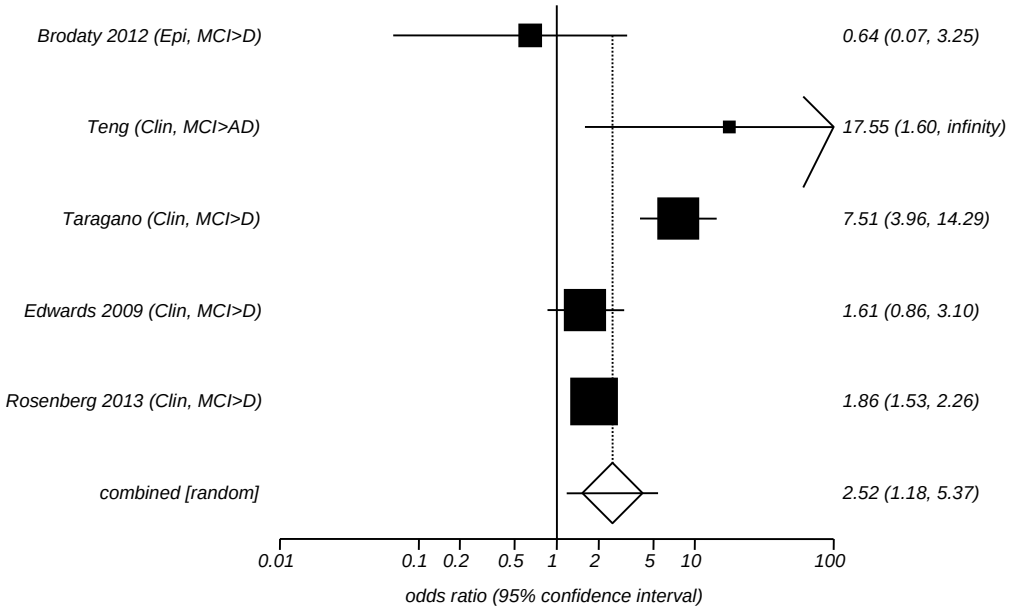
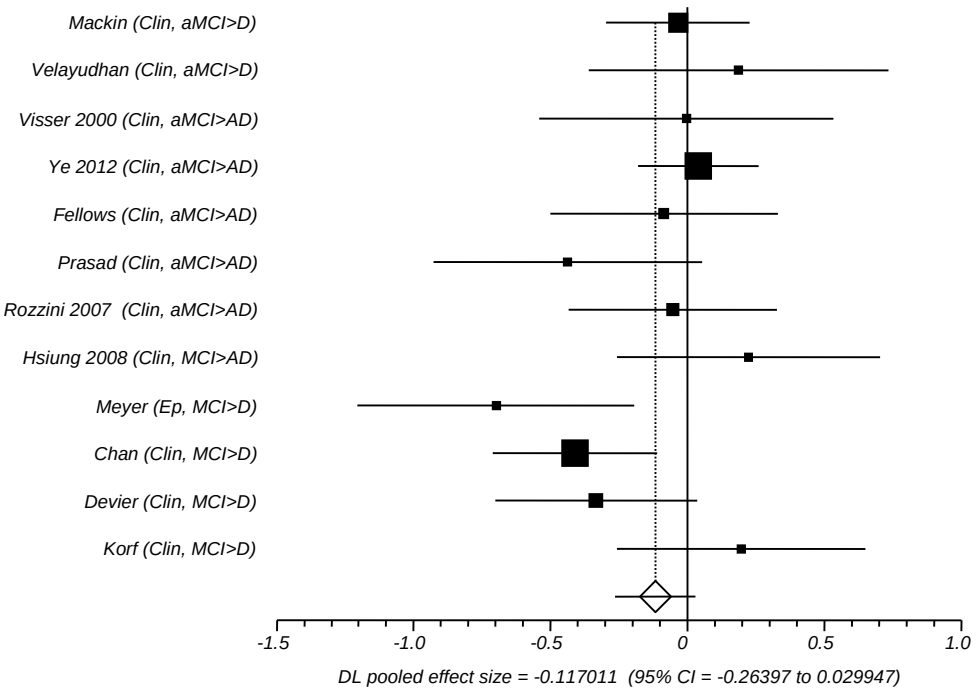


Figure 2g: Effect size for years of education



Key for all tables

Unless stated, dementia diagnoses met DSM-IV (or DSM-IIIR) criteria for dementia, or NINCDS/ARDRA criteria for possible or probable AD, or NINDS-AIREN criteria for possible or probable vascular dementia, or DLB Consortium criteria for Lewy body disease or Manchester-Lund criteria for frontotemporal dementia

***MCI criteria for diagnosis – in addition to objective cognitive (or for aMCI) impairment on testing; absence of dementia and ADL impairment**

**** Whether meets validity criteria in method: 1. A defined representative sample of participants assembled at a common (usually early) 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.Participant follow-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.**

AB= abstinence; AD=Alzheimer's Disease; ADASCog= Alzheimer's Disease Assessment Scale-cognitive subscale; ADL= Activities of Daily Living; aMCI= Amnestic Mild Cognitive Impairment; APOE=Apolipoprotein E; b/l= baseline; BMI= Body Mass Index; bp= Blood Pressure; CDR=Clinical Dementia Rating scale; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; CAD= coronary artery disease; ChEI= Cholinesterase Inhibitor; C/NC: Converters (to Dementia) versus Non-Converters; CPH= Cox Proportional Hazards; CSF= Cerebrospinal Fluid; CIRS=Cumulative Illness Rating Scale; CVA= Cerebrovascular Accident; DM= Diabetes Mellitus; FHx= Family History of Dementia; GDS=Geriatric Depression Scale; GLM= Generalized Linear Model; HD=Heart disease; HDL= High Density Lipoprotein; HR=Hazard Ratio; HRT= Hormone replacement Therapy; HT=Hypertension; IADL= Instrumental Activities of Daily Living; IQ= Intelligence Quotient; IWG=International Working Group; KM= Kaplan-Meier analysis; LDL= Low Density Lipoprotein; LEDS=Life events and Difficulties Schedule; LR= Logistic Regression; MCI=Mild Cognitive Impairment; MMSE=Mini Mental State Examination; MADRS=Montgomery–Åsberg Depression Rating Scale; MD-MCI= Multi domain MCI; MeDi= Mediterranean Diet; MPS= Mild Parkinsonian Symptoms; N= number; NINCDS=National Institute of Neurological and Communicative Disorders and Stroke; NP= Neuropsychological test score; NPI= Neuropsychiatric Inventory; NS= Non Significant; OR=Odds Ratio; (P)= Petersen criteria; CT=Randomised Controlled Trial; RR= Risk or Rate Ratio; SD= Standard Deviation; SMC=Subjective memory impairment; S/IMC= Subjective or informant base memory impairment; SCC=Subjective cognitive complaint; S/ICC= Subjective or informant-based cognitive complaint; T1/T2 = Time 1 and Time 2; TIA= Transient Ischemic Attack; UC: Univariate comparisons; VaD=Vascular Dementia; WMS-R=Wechsler Memory Scale-Revised; WS= Figure shows response or follow-up rate for whole cohort, not specifically those with MCI

Table 1: Characteristics and findings of higher quality epidemiological studies

Study	Recruitment source	% recruited	FU, years	MCI subtypes and criteria*	N (outcome if not dementia)	% follow-up	Analysis adjusted for..	Model	Prognostic factor	Statistics (for all MCI unless stated)
Han [73]	Random sampling in Seongnam, Korea	64%	1.5	All IWG criteria	140	71%	age, sex, education, time, APOE, medications,MMSE, GDS, CIRS	LR	Years education, chronic illness, GDS, medications	All ns (stats not given)
Li [18]	Long term residents aged 55+ without depression from 10 randomly selected communities in the city of Chongqing	71%	5	aMCI SMC	638 (AD)	76%	age, sex, education, occupation, depressive symptoms, APOE4, baseline MMSE, and ADL score	CPH	**Hypertension**	**HR 1.84(1.19–2.84) p=0.006**
									Diabetes	**HR 1.62 (1.00–2.62) p=0.049**
									Hypercholesterolemia (HC)	**HR 1.11 (1.04–1.18), p=0.001**
									Obesity	HR 1.15 (0.45–2.92) p=0.78
									Myocardial infarction	HR 1.05 (0.67–1.65) p=0.83
									Atrial fibrillation	HR 1.09 (0.54–2.20) p=0.815
									Current smoking	HR 1.09 (0.67–1.79) p=0.73
									Daily drinking	HR 1.10 (0.69–1.75) p=0.700
									Vs untreated: HT treated	**HR 0.85 (0.80–0.90) p=0.001**
									Diabetes treated	**HR 0.87 (0.83–0.91) p=0.001**

									HC treated	**HR 0.88 (0.83–0.93) p=0.001**
									Cease smoking	HR 0.91 (0.49–1.70) p=0.78
									Cease drinking	HR 0.89 (0.62–1.27) p=0.51
Luck [25]	A random sample selected from people aged 75+ in 6 German towns referred by General Practitioners	75%	4.5	All	745	71%	Age, gender, cognition and other factors listed	CPH	Living alone	HR 1.42 (0.95–2.14) 0.09
									Not married currently	HR 1.52 (0.71–3.23
									Diabetes Mellitus	HR 1.35 (0.94–1.96) 0.11
									Hypertension	HR 1.05 (0.70–1.59) 0.81
									Cardiac arrhythmia	HR 0.80 (0.53–1.21) 0.30
									Coronary heart disease	HR 1.25 (0.82–1.90) 0.29
									Myocardial infarction	HR 0.59 (0.31–1.15) 0.12
									Peripheral artery disease	HR 0.95 (0.53–1.69) 0.85
									Carotid artery stenosis	HR 0.61 (0.21–1.79) 0.37
									TIA	HR 1.55 (0.91–2.64) 0.10
									Hyperlipidaemia	HR 1.27 (0.82–1.95) 0.29
									Hypercholesterolemia	HR 1.16 (0.76–1.78) 0.48
									Epilepsy	HR 0.14 (0.02–1.12) 0.06
									Hyperthyroidism	HR 0.94 (0.45–1.96) 0.87

									Hypothyroidism	HR 0.88 (0.34–2.32) 0.80
									GDS 6+	**HR 1.60 (1.03–2.48) 0.04**
									Impaired vision	HR 1.02 (0.65–1.58) 0.95
									Impaired hearing	HR 1.44 (1.01–2.05) 0.05
									Former vs non-smoker	HR 0.69 (0.45–1.08) 0.10
									Current vs non-smoker	HR 0.94 (0.47–1.87) 0.86
									Normal vs no drinking	HR 1.13 (0.78–1.65) 0.51
									Harmful vs no drinking	HR 0.47 (0.06–3.59) 0.46
									Antidementia drugs	HR 1.19 (0.78–1.84) 0.42
Peltz [78]	Members of a large USA retirement community, aged 90+	61%	2.5	All	395	94%	Age	CPH	Education (being college graduate)	HR 1.03 (0.6–1.6)
Richard[102]	Participants identified from a probability sample of Medicare beneficiaries in New York 1999-2001	98.9 %	5.1	All MCI SMC	320	74%	Age, sex education, ethnicity	CPH	Depression (CES-D 4+)	HR 1.8 (1.0-3.1)
Scarmeas [61]	Participants identified (via ethnicity and age stratification) from a Medicare probability sample of beneficiaries in New York in 1992 and 1999	64%	4.3	aMCI all SMC	482 (AD)	85%	cohort, age, sex, ethnicity, education, APOE, caloric intake, BMI,	CPH	**Middle vs lowest MeDi adherence tertile**	**aMCI/MCI: HR 0.48 (0.22-1.04; P=.06); HR=0.55 (0.34-0.90); P=.01**
									Highest vs lowest tertile	**aMCI/MCI: 0.71 (0.32-1.59) P=.41; 0.52 (0.30-0.91) P=.02**

Panza [103]	Data from Italian Longitudinal Study of aging, a random sample population survey of people aged 65-84 from 8 municipalities	83%	3.5	aMCI normal MMSE for age/ education	121	87%	Sex, age, education, HT, CAD, smoking, stroke, DM, HC	Poisson	Italian GDS 10+	Rate ratio 1.42 (0.48–4.23)
Solfrizzi [39]							Gender, age education	CPH	**<1 drinks /day alcohol vs abstinence (AB)**	**HR 0.15 (0.03–0.78)**
									1-2 drinks/day vs AB	HR 0.47 (0.08–2.73)
									2+ drinks/day vs AB	HR 0.44 (0.05–4.06)
									<1 drinks /day wine vs AB	**HR 0.15 (0.03–0.77)**
									1-2 drinks/day wine vs AB	HR 0.44 (0.07–2.64)
									2+ drinks/day wine vs AB	HR 0.36 (0.03–4.26)
Solfrizzi [41]							Sex, age, education, GDS, alcohol, smoking, fibrinogen, cholesterol, HD, stroke	CPH	**Metabolic syndrome**	**HR 7.80 (1.29–47.20)**
Solfrizzi [24]							None	Univariate Poisson regression	Education (<4 years)	RR 0.79 (0.23–3.44)
									No hypertension	RR 1.74 0.46–9.74
									No coronary artery disease	RR 1.71 0.32–6.78
									No type II DM	RR 0.54 0.01–3.62
									Never smoked	RR 0.46 0.08–1.74
									Cholesterol, vs <4.5: 4.6–5.2	RR 0.75 0.11–4.43
									5.2-6.0	RR 0.97 0.18–5.20
									>6.0	RR 0.75 0.11–4.43
									HDL cholesterol (vs <1.0): 1.0–1.2	RR 1.37 0.27–8.84
									1.2–1.4	RR 1.67 0.32–10.73
									>1.4	RR 0.30 0.01–3.75

St John[72]	Random sample of residents aged 65+ of Manitoba, Canada	61%	5	All; Modified MMSE < 78, CIND on exam	85	90%	Sex, age, education, MMSE, depression, function, SMC	LR	self-rated health good	OR 1.05 (0.30- 3.72)
									Educations (years)	OR 0.88 (0.74- 1.05)
Caracciolo[104]	Kungsholmen Project, population-based prospective cohort study of all registered inhabitants aged 75+ in a Stockholm district, Sweden, in 1987	76%	3	All, aMCI, Non aMCI	160	85%	age, sex, education and APOE	CPH	Perceived sadness/ low mood at baseline	**aMCI: HR 5.9 (1.4 to 25.0)** All MCI: 1.4 (0.8 to 2.4)
Xu[22]			9		302	90%	age, sex, education, MMSE, survival, BMI, HD, stroke, bp, APOE antihypertensive drugs	CPH	**Prediabetes (blood glucose 7.8 –11.0 mmol/l)**	**Dementia: HR 4.96 (2.27–10.84); AD: 5.73 (2.43–13.5)**
									Diabetes Mellitus	**HR 2.87 (1.30–6.34) AD: HR 2.83 (1.18–6.78)**
									DM or preDM	**aMCI: HR 2.24 (0.75–6.71) non a-MCI: 4.31 (1.97–9.42)**
Palmer[60]			3	aMCI MMSE >19; SMC	47 (AD)	92.4 % WS	age, sex, and education		Mood symptoms	RR 0.9 (0.6–1.5)
									Motivation symptoms	RR 1.1 (0.7–1.8)
									Anxiety symptoms	**RR 1.8 (1.2–2.7)**

Table 2: Characteristics and findings for other epidemiological studies

Study	Recruitment source	FU, years	N	Type of MCI	Outcome	Analysis adjusted for..	Model	Prognostic factor	Statistics	Validity*		
										1	2	3
Artero[26]	Random sample recruited from French electoral roles	4	2882	All IWG criteria S/ICC	Dementia	None	** UC , LR	Hypertension; coffee, alcohol, tobacco use; HRT Hypercholesterolaemia; head trauma; depression; herpes; anaesthesia; cancer; diabetes, vascular risks, asthma, antidepressants, subjective health, insomnia, BMI >27, appetite loss, social isolation,	Not significant on univariate comparisons for men or women (p>0.01; actual stats not shown)	n	y	y
						IADL APOE Age Stroke (men) Gender-stratified		**Subclinical depression**	**Women: OR 1.95 (1.06-3.58); p<0.03 Men NS**			
								Anticholinergic drugs	**Women: OR 1.78 (1.00 -3.18) p=0.04; Men: NS**			
								Low education level	**Men: OR 2.26 (1.25 to 4.06); p<0.01; Women: 2.16 (1.31 to 3.56); p<0.01**			
Blasko [62]	People recruited for a population-based study of	5	81		Dementia	none	LR	**Self-reported folate/B12 supplements vs (1)**	**(1) OR 0.15, 0.03-0.77 p=0.023** (2) OR 1.8 (0.6-5.6), p=0.330	**n**	**y**	**y**

	75 year-olds in Vienna, Austria							**non-users** (2) inconsistent users				
								Serum homocysteine and B12 levels	Not significant			
						sex, APOE, education, creatinine, folate	LR	**Ln of serum folate**	**OR 0.17 (0.04-0.69), p=0.013**	**n**	**y**	**y**
								Education (years)	OR 0.77 (0.58-1.01), p=0.062			
Brodaty[47]	70–90 years on Sydney electoral roll	2	319	All (P)	Dementia	age, sex, education	LR	NPI score >=1	OR 0.57 (0.1–2.8), p=0.49	n	y	y
Beaudreau[45]	Adults aged 70+ in USA aging study recruited to represent population	4	180	All, panel diagnosis	Dementia	Age , APOE Education, NPI	LR	Education (years)	OR 0.97 (0.88, 1.07) p=0.56	n	y	y
								NPI total scores	OR 1.01 (0.97, 1.06) p=0.61			
Chan et al[59]	People aged 60+ from Hong Kong, and from old age hostels & day centres	2	321	All SMC	Dementia	MMSE, education, age, gender	LR	Education (years)	OR 0.98 (0.87–1.09) p=0.67	n	y	y
								depression/dysphoria	**OR 2.40 (1.05–5.46) p=0.04**			
								apathy/indifference	OR 0.31 (0.09–1.13) p=0.08			
								aberrant motor behaviour	OR 9.96 (0.57–174.42) p=0.12			
Lopez [105]	Random sampling of Pittsburgh Medicare	Mean 4.3	136	aMCI and MD-MCI		Nil	**UC	> High school education, No. (%)	NS, chi2=2.43	n	y	y
Meyer [80]	Participants who developed MCI during longitudinal study	mean 3.9	73	SMC All	AD and vascular dementia	None	**UC	**Education (years)**	**AD, C/NC: 11.54 vs 14.57, p<0.01 VaD, C/NC: 13.13 vs 14.57**	**n**	**y**	**y**

Oveisgharan [30]	Participants in Canadian Study of Ageing, recruited to represent population	5	990	All	Dementia	Age, sex, APOE, cognitive impairment subtypes and interaction terms	LR	Hypertension	NS (results not given); in subgroup with executive dysfunction, hypertension, 57.7% vs normotension 28.0%,P=.02), in UC	y	n	y

Table 3: Characteristics and findings for clinical studies

Study	Recruitment source	FU, years	N	Type of MCI	Outcome	Analysis adjusted for..	Model	Prognostic factor	Statistics	Validity (see method)		
										1	2	3
Abner [29]	Recruits from Kentucky AD center who entered a longitudinal study (BRAiNS) , who agreed to brain donation, when cognitively intact and developed MCI	10	101	All, aMCIS/ICC, Intact global cognition	Dementia	APOE, age, gender, family history, education, hypertension, MCI duration	Markov chain	**Hypertension**	**RR 0.30 (0.10–0.93)**	n	y	y
Abner[37]			649					**Vs never smoked: <1 – 10 pack-years vs. never smoked**	**OR 0.28 (0.08–0.94) p= 0.039**	n	y	y
								10-20 pack-years	**OR 0.28 (0.08–0.94) 0.04**	n	y	y
								⩾20 pack-years	**OR 0.31 (0.13-0.71) p=0.005**	n	y	y
Kryscio[75]			554		Dementia	APOE, age, gender, family history, education	polytomous LR	⩽12 vs ⩾16 years education	Amnestic: OR 1.00 (0.32–3.14) Mixed: 0.38 (.05–3.12)	n	y	y
								13-15 vs ⩾16 years education	Amnestic: OR 0.92 (0.39–2.16)Mixed: 1.56 (0.64–3.79)	n	y	y
Kryscio[36]							Years to diagnosis	**HRT**	**Mean (SD) 1.3±0.5, p=0.0029**	n	y	y
								Smoker at baseline	**0.66±0.26, p=0.043**	n	y	y
Alefret[68]	Clinical convenience sample	4	42	aMCI(P)	AD	Age, gender	CPH	2ndry school education	HR 1.80 (0.70–4.67)	n	y	y
Amieva[70]	Participants in drug RCT, no history of depression or stroke	2	90	SMC aMCI	Dementia	-	**UC	% primary school diploma	C/NC 89.7% vs 88.5% (p=0.99)	n	y	y
Aretouli et al [76]	Research centers and clinics in USA	2	104	All	Dementia (CDR ⩾1)	-	**UC	Education (years)	F(1,92)=0.02, p=.890	n	y	y

Barabash[69]	Consecutive, Madrid Memory Unit	1.7	89	aMCI, SMC	AD	Age, APOE, genetics	CPH	**< 10 years schooling**	**HR 0.23 (0.05–0.98) p=0.016**	n	y	y
Betterman[106]	Recruited from 4 USA academic centres	6	482	All	Dementia (expert panel)	age, sex, race, APOE, education, stroke, HD	CPH	Statin ever	HR 0.88 (0.64-1.21) p=.43	n	y	y
								Other lipid lowerer	HR 0.78 (0.36-1.68), p= .52			
Brodaty[42]	9 Australian memory clinics	3	185	All (P)	Dementia	Age, sex, MMSE	CPH	Depression (NPI subscale)	HR 1.08 (0.98-1.19)			
								NPI (total & 6 m change)	Not significant, results not given			
Chilovi et al[58]	Outpatient aging clinic, Brescia, Italy	2	124	All S/ICC	Dementia	Age, Barthel Index, ADAS-Cog	LR	**Clinical depression**	**OR 0.10 (0.02–0.39); p=0.001**	n	y	y
								Clinically significant apathy	**OR 7.07 (1.99–25.17); p=0.003**			
Devanand[67]	New York Memory clinic attendees, without psychiatric diagnosis or CVA	4.5	139	All SMC	Dementia	-	**UC	Education (years)	C/NC: mean 14.1(SD 4.5) vs 15.6 (4.0)	n	y	y
Devier[53]		1-9	108 148	aMCI All ; SMC	AD	Cognition, education and stratified for age (and other variables tested)	CPH	State anxiety	HR 1.68 (0.75- 3.77) p=0.21	n	y	y
								Trait anxiety	**aMCI: 0.35 (0.14- 0.85) p=0.02 All MCI: HR 0.36 (0.16- 0.82) p=0.015**			
								Hamilton depression score	All MCI: HR 1.01 (0.92-1.10) p=0.86 aMCI NS (results not given)			
								Education (years)	HR 1.01 (0.93, 1.10) p=0.81			
Edwards[49]	Records, Californian memory clinics	1.6	270	All	Dementia	Age, MMSE, function, site, comorbidity	LR	**4+ neuropsychiatric symptoms**	**OR=2.44 (1.07–5.55)**	n	n	y

Farias [74]	Clinic referrals and outreach	2	1111	All	Dementia	memory, age, education	CPH	Education (years)	NS	n	y	y
Fellows [38]	Canadian memory clinic	3.3	90	aMCI S/IMC	AD	age onset, MMSE, sex, education, function	UC; LR	Smoking (pack years)	OR 0.98 (0.95-1.00) p=0.13	n	y	y
						None	**UC	Education (years)	C/NC: (mean(SD): 10.6 (3.6) vs 10.9 (3.3)	n	y	y
								GeDS >6	C/NC 55 vs 62, p=0.53			
								Alcohol consumption	C/NC 45 vs 44, p=0.92			
								Vascular risk factors	C/NC 60 vs 45 p=0.15			
Fleischer [107]	Participants in an RCT	3	539	aMCI	AD	Age, sex, cognition, FHx	GLM	Education (years)	NS	n	y	y
Gabryelewicz [52]	Participants in a longitudinal study recruited from consecutive referrals to Warsaw clinic MADRS score 28 or less	3	105	All SMC	Dementia	Age	ANCOVA	**Higher baseline MADRS score**	**F=4.83, p=0.010**	n	y	n
Gavrilova [64]								**Higher baseline homocysteine levels**	**MD-MCI: 16.53 umol/l vs 14.36 umol/l; U=713, P=0.037 aMCI: ns**			
Grande[82]	Milan (Italy) memory clinic	Median 2.6	176	All SCC	Dementia	age, gender, education, MMSE, GDS, MCI subtype, APOE	CPH	Physical activity score (vs lowest tertile): middle 3le	HR 0.59 (0.32 to 1.10)	n	y	y
								Highest tertile	**HR 0.36 (0.18 to 0.75)**			
								Social activity score (vs lowest tertile): middle 3le	HR 0.82 (0.54 to 2.15)			
								Highest tertile	HR 0.42 (0.68 to 2.56)			
								Cognitive activity score (vs lowest tertile): middle 3le	HR 0.54 (0.26 to 1.14)			
								Highest tertile	HR 0.89 (0.45 to 1.77)			

Ravaglia [27]	Bologna (Italy) geriatric clinic attendees aged 60+ with reliable informant, without psychiatric disorder recruited from March 1999 to March 2004 and August 2005 (Forti	Mean 2.8	165	All S/IMC MMSE >23	Dementia, deficits in 2+ cognitive domains affecting functioning	Age, gender, education	CPH	Ever smoking	HR 0.54 (0.22–1.32) p<0.177	n	y	y
								Diastolic bp (-10mmHg)	**HR 0.56 (0.39–0.80) p<0.001**			
								Systolic (-10mmHg)	**HR 0.81 (0.69–0.95) p<0.013**			
								Hypertension	HR 1.25 (0.70–2.45) p<0.453			
								BMI (vs 25.1-27.6): <25	**HR 2.07 (1.04–4.14) p<0.039**			
								27.7–29.9	HR 0.53 (0.20–1.37) p=0.189			
								>30	HR 0.62 (0.26–1.46) p=0.270			
								Diabetes	HR 0.75 (0.26–2.13) p<0.593			
								Cardiovascular disease	HR 0.90 (0.44–1.84) p<0.780			
								Chol (Ref 5.3–6.): <5.3:	HR 1.78 (0.85–3.70) p=0.123			
								6.0-6.5 mmol/l	HR 0.38 (0.13–1.07) p=0.068			
								>6.5 mmol/l	**HR 0.29 (0.09–0.87) p=0.028**			
								Vitamin B12 ⩽217 pmol/l	HR 0.60 (0.26–1.39) p=0.234			
								Serum folate ⩽ 10.4 nmol/l	**HR 2.23 (1.12–4.43) p=0.022**			
Forti [83]			180			+ MMSE, bp, BMI, folate	CPH	**Atrial fibrillation**	**HR 4.63 (1.72-12.46) p<0.002**	n	y	y
						None	**UC	Education >5 years	C/NC: 14 (26.9) vs 29(22.6) p=0.54	n	y	y

Maioli [34]		1.2	52			None	**UC	Serum HDL mg/dl	C/NC 70(25) vs 58 (13), p=0.058	n	y	y
								Serum LDL mg/dl	C/NC: 106 (42) vs 122 (52) p=0.359			
Hansson [32]	Attendees from a Swedish memory clinic, who agreed to provide a sample of CSF	4	137	aMCI SMC	AD	age, sex, education level, APOE ε4	CPH	Received higher education	HR 0·80 (0·45–1·43)	n	y	y
								Systolic bp	HR 1·00 (0·98–1·01)			
								Diastolic bp	HR 0·99 (0·97–1·02)			
								Homocysteine	**HR 1·08 (1·04–1·12)**			
Hsiung [43;108]	Recruited from 8 Canadian memory clinics	2	68	All; MCI on exam	AD, VaD	age, sex	LR	**Education (years)**	**AD: OR 0.82 (.76–.89) VaD: 0.62 (.49–.79)**	n	n	y
							**UC	NPI	C/NC: 4.3(6.3) vs 11.0 (20.1)	n	n	y
								Chronic medical illness	C/NC 5.2 (4.3) vs 5.3 (3.9)			
Jack [28]	Consecutive patients 60-89 from Mayo clinic research registry	2.7	80	S/IMC aMCI	AD	none	nonparametric CPH	Hypertension	RR 1.63 p=0.272	n	y	y
								Ischemic heart disease	RR 0.55 p=0.272			
								Estrogen replacement	RR 1.09 p=0.864			
Korf [31]	Consecutive attenders at a geriatric clinic, Stockholm, Sweden	2.8	75	All	Dementia	time	CPH	Education (years)	HR 0.93 (0.82–1.06)	n	y	y
								Hypertension	HR 0.62 (0.27–1.42)			
								Depression	HR 0.76 (0.38–1.52)			
Lee [81]	Aged 55+, ⩾1 FU, South Korean study	1.47	504	All; SCC	AD	Age, MMSE score	CPH	**Education (years)**	**HR 1.08 (1.04–1.13) p<0.001**	n	y	y
Li [19]	Inpatients in a Chinese hospital those with CVA or depressive disorder excluded	3	257	aMCI SMC	AD	Age, covariates listed; carotid stenosis, stroke during follow-up and white matter changes	CPH	**diabetes mellitus**	**HR 2.39 (1.07–5.33) p=0.03**	n	y	y
								Education (> 6 years)	HR 0.48 (0.21–1.10) p=0.08			
								Hypertension	HR 0.71 (0.22–2.22) p=0.55			

								Antihypertensives	HR 1.22 (0.48–3.13) 0.68			
								antihyperglycemic	HR 2.08 (0.66–6.54) p=0.21			
Luis [109]	Record review Miami memory clinic	2.4	134	All SCC	Dementia	Age, sex, MMSE, subtype	CPH	Education (years)	NS (results not given)	n	y	y
Mauri [110]	Italian outpatient clinic patients	3	119	All	Dementia	None	No tests	**Mild parkinsonism symptoms at baseline**	**11/22 (50%) with MPS at baseline and 35/97 without developed dementia; trend (p<0.05) for vascular dementia**	n	y	y
Modrego [51]	Consecutive Spanish outpatient clinic patients	3	114	aMCI SMC	Dementia	None	Log rank test	**Depression diagnosed by structured clinical interview**	**HR: 4.1; 2.4-6.9**	n	y	y
Olazaran [77]	Recruited by primary care physicians in a Madrid practice	1	81	All	Dementia	Age, sex	LR	**Higher educational level (not illiterate or incomplete education)**	**OR 0.13 (0.02–0.77) 0.024**	n	y	y
Palmer[56]	Consecutive new diagnoses at 3 Rome memory clinics	4	131	aMCI	AD	age, sex, apathy, MMSE, education, depression	CPH	Depression diagnosis	HR 0.6 (0.2–1.8)	n	y	y
								Apathy diagnosis	**HR 6.9 (2.3–20.6)**			
								NPI apathy score 2+	**HR=4.6 (1.3−16.2)**			
Peavy [111]	Research centre & clinic, aged 65+, no mental illness, 3 follow-ups	2.5	33	All (P)	Dementia	Age, gender, education, cortisol, APOE	LR	Education (years)	NS (data not shown)	n	y	y
Perri [112]	Aged 50-80, USA memory clinics, ⩾5 years education	2	190	aMCI S+IMC	AD	Age, gender, cognition	LR	Education (years)	NS (p=0.85)	n	y	y
Prasad [20]	Patients at a tertiary neurology memory clinic with follow-up information	1.5	79	aMCI Petersen criteria	Dementia (all AD)	none	**UC	Education (years)	C/NC: 8.3 vs10.2 p = 0.098	n	n	y
								Diabetes mellitus	C/NC: n=10 (43.5%) vs 15 (28.9) p=0.215			

	available for 18 months including MRI scans							Hypertension	C/NC: 11 (47.8) vs 28 (52.8) p=0.094			
								Hyperlipidemia	**C/NC: 10 (45.4) vs 36 (67.9) p=0.032**			
Mackin [35]	ADNI database, recruited from 50+ sites in USA and Canada without depression (GDS<6)	2-3	405	aMCI S+IMC MMSE >23	AD	ApoE, intracranial volume, white matter lesions, demographics removed as NS	CPH	**GDS score 1-5 (sub syndromal depression) vs GDS=0**	**NS (statistics not given)**	n	y	y
		3	227	SMC aMCI	Dementia (NINCDS)	None	**UC	Education (years)	C/NC: 15.9 (2.9) vs 16.0 (2.8) p=0.72	n	n	y
								GeDS 6+ at follow-up	OR = 1.88, p = 0.15			
								GeDS score	C/NC: 1.6 (1.3) vs 1.5 (1.4) p=0.38			
								Serum LDL mg/dl	C/NC:106 (42) vs 122 (52) p=0.359			
Morris[21]		2	264			Education, age, sex	ANOVA	**Impaired glycaemia**	**C/NC:48.5% vs 32.3% p=0.009**	n	y	y
Richard [55]		mean 2.7	151			age, gender, education and baseline MMSE score	CPH	**Apathy symptoms**	**HR 1.85 (1.09–3.15)**	n	y	y
			219					CES-D score 4+	HR 1.15 (0.72–1.83)			
			211					Apathy and depression	HR 1.05 (0.91–1.23)			
Schneider [84]		2	402			age, APOE, education ADAS-cog score	Weibull R	**ChEI vs no treatment**	**29.8% reduced time to dementia (P=.005)**	n	y	y
								ChEI and memantine	**41.8% reduced time to dementia (P=.003)**			
Robert [57]	Patients from 14 French memory clinics aged 58+, >4 years education, with informant; not MADRS score >20 or significant brain vascular change	1	216	aMCI SMC MMSE >24	AD	age, sex, educational level, MADRS total score and Goldberg anxiety scale	LR	Psychiatric history	C/NC 31.8 vs 19.7, p=0.16	n	y	y
								Education (% tertiary)	C/NC 31.8 vs 44.3, p=0.22			
								Goldberg anxiety scale	C/NC 2.6 (2.5) vs 2.9 (2.5) p=0.16			

								MADRS total score (% >10)	C/NC 31.8 vs 18.6, p=0.26			
								Apathy	C/NC 59.1 vs 37.6, p=0.10			
Rosenberg [50]	Data from National Alzheimer Coordinating Center database, USA	Median 1.58	1821	All Expert diagnosis	Dementia AD	Cognition, age, ethnicity	CPH	**NPI middle vs lowest tertile**	**Dementia/AD: HR 1.43 (1.15–1.80) p=0.002/ 1.48 (1.17–1.88) p=0.001**	n	n	y
								NPI top vs lowest tertile	**HR 1.5(1.2–1.9)<.001/1.4(1.1–1.7) .013**			
								GDS mid vs lowest tertile	**HR 1.4 (1.1–1.7) .003 / 1.3 (1.0–1.6) p=0.05**			
								GDS top vs lowest tertile	**HR 1.37 (1.1–1.71) p=0.01**/1.17 (.92–1.5)p=.21			
Rozzini [113]	Consecutive referrals to Italian memory clinic	2	46	Not stated	Dementia	None	**UC	Depression diagnosis at baseline	17/24 without depression developed dementia vs 8/22 with depression	n	y	y
Rozzini [44]		1	119	aMCI S/IMC	AD	None	**UC	Education (years)	NS	n	y	y
								NPI	C/NC: 14.5 (11.2) vs 12.6 (10.7) NS			
								GeDS	C/NC: 4.3 (3.6) vs 4.7 (3.1) NS			
								Hamilton anxiety scale	C/NC: 8.5 (6.4) vs 10.4 (6.5)			
								Number of drugs	C/NC: 2.8 (2.2) vs 2.5 (1.8)			
Sachdev [79]	Patients at two Australian hospitals , 3-6 months after ischaemic stroke / TIA	3	45	All	Vascular dementia	None	**UC	Education (years)	NS (stats not given)	n	n	y

Siuda [63]	Polish Neurology outpatient clinic	1	55	SMC Objective cognitive imp	Dementia	None	**UC	Total homocysteine (µmol/L)	C/NC: 19.83 (7.31) vs 19.85 (7.64) p=0.645	n	y	y
								Vitamin B12 (pg/mL)	C/NC: 376.11 (173.44) vs 495.32 (335.78) p=0.143			
								Folic acid (ng/mL)	C/NC: 3.60 (1.72) vs 3.75 (1.90) p=0.752			
Squitti[65]	Italian memory clinic, GDS <14	2-6	141	aMCI	AD	Age, gender, MMSE	CPH	Serum Nonceruloplasmin Copper	HR 1.23 (1.03–1.47), p=0.022	n	y	y
								transferrin, ferritin hypercholesterolemia, hypertension	Not significant (data not shown)			
Taragano [48]	Consecutive patients, Argentinian clinic	5	239	Any SCC	Dementia	None stated	CPH	**Psychiatric symptoms**	**HR 4.01 (2.5-6.3)**	n	y	y
Teng [46]	Memory clinic patients aged 50+	2	51	Any SCC	AD	MMSE, subtype, sex	ANCOVA	**Any neuropsychiatric symptoms**	**F(1, 40) = 5.23 p=.028**	n	y	y
Velayudhan [23]	People aged 65+ primary care practices in south London, UK	4	61	aMCI SMC	Dementia	Age, gender, APOE, IQ, education, smoking, health	CPH	**Diabetes**	**HR 2.9 (1.1–7.3)**	n	y	y
								Duration of diabetes	HR 0.9 (0.7–1.1) 0.29			
						None		Depression	HR 1.4 (0.5–3.9) p=0.5	n	y	y
								Education	HR 1.0 (0.9–1.2) p=0.61			
								Coronary heart disease	HR 1.1 (0.4–2.8) p=0.85			
								Drinking alcohol	HR 2.6 (0.7–8.8) p-0.1			
								Lifetime smoking status	HR 0.8 (0.17–4.3) p=0.8			
Visser [114]		10	64	SMC aMCI	Dementia	-	**UC	Education (years)	chi2<1.4, *p* >0.23	n	y	y

Visser [54]	new consecutive patients, Maastricht memory clinic without vascular MCI	5	74	SMC aMCI	Dementia (All AD)	-	**UC	Education (years)	C/NC: 10.3 (3.6) vs 11.2(2.6) NS	n	y	y
								Depression (baseline)	C/NC: 26% vs 50%, NS			
								Depression (follow-up)	C/NC: 7% vs 29% NS			
Xu [40]	Male patients from 2 Chinese neurology outpatient clinics	2	163	SMC any	Dementia	-	KM	**Heavy vs light to moderate alcohol use**	**P<0.05**	n	y	y
								Heavy drinkers vs abstainers	**P<0.05**			
Yasar[33]	Participants with MCI in USA RCT of Ginkgo Biloba	6.1	320	All	AD	age, sex, education, income, no. of vascular diseases, BMI	CPH	**Diuretic vs no antihypertensive use**	**HR 0.38 (0.20–0.73) 0.004**	n	y	y
								Other cardiovascular drugs	Not significant predictors			
Ye [71]	Consecutive patients in 31 South Korea memory clinics	Mean 1.43	249	aMCI SMC	AD	age, gender, and baseline MMSE	CPH	**Education (>8 years)**	**HR 2.18 (1.10–4.32); Late-stage: 2.38; p =0.03** Early: NS	n	y	y
Ye [66]	People in National USA MRI study	4	319	aMCI SMC	Probable AD	-	**UC	Education (years)	C/NC: 15.77 ± 2.90 vs 15.65 ± 3.06, p=0.7	n	y	y

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