RESEARCH PAPER

Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis of cohort studies

Jie-Qiong Li,[1] Lan Tan,[1,2,3] Hui-Fu Wang,[2] Meng-Shan Tan,[3] Lin Tan,[3] Wei Xu,[1] Qing-Fei Zhao,[1] Jun Wang,[1] Teng Jiang,[2] Jin-Tai Yu[1,2,3,4]

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[1]Department of Neurology, Qingdao Municipal Hospital, School of Medicine, Qingdao University, Qingdao, China
[2]Department of Neurology, Qingdao Municipal Hospital, Nanjing Medical University, Qingdao, China
[3]College of Medicine and Pharmaceutics, Ocean University of China, Qingdao, China
[4]Department of Neurology, Memory and Aging Center, University of California, San Francisco, California, USA

Correspondence to
Dr Jin-Tai Yu, Department of Neurology, Memory and Aging Center, University of California, 675 Nelson Rising Lane, Suite 190, Box 1207, San Francisco, CA 94158, USA;
yu-jintai@163.com

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ABSTRACT

Objective We sought to identify the risk factors for predicting the progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD).

Methods We searched 6 electronic databases for cohort studies published from January 1966 to March 2015. Eligible studies were required to be relevant to the subject and provide sufficient data for our needs.

Results 60 cohort studies with 14 821 participants from 16 countries were included in the meta-analysis. The strongest positive associations between risk factors and the progression from MCI to AD were found for abnormal cerebrospinal fluid (CSF), phosphorylated τ (p-τ) (relative risk (RR)=2.43, 95% CI=1.70 to 3.48), abnormal CSF τ/Aβ_{1-42} (RR=3.77, 95% CI=2.34 to 6.09), hippocampal atrophy (RR=2.59, 95% CI=1.95 to 3.44), medial temporal lobe atrophy (RR=2.11, 95% CI=1.70 to 2.63) and entorhinal atrophy (RR=2.03, 95% CI=1.57 to 2.62). Further positive associations were found for the presence of apolipoprotein E (APOE) ε4ε4 and at least 1 APOEε4 allele, CSF total-τ (t-τ), white matter hyperintensity volume, depression, diabetes, hypertension, older age, female gender, lower mini-mental state examination (MMSE) score and higher AD assessment scale cognitive subscale (ADAS-cog) score. Negative associations were found for high body mass index (RR=0.85, 95% CI=0.76 to 0.96) and higher auditory verbal learning test delay score (RR=0.86, 95% CI=0.77 to 0.96).

Conclusions Patients with MCI with APOEε4, abnormal CSF τ level, hippocampal and medial temporal lobe atrophy, entorhinal atrophy, depression, diabetes, hypertension, older age, female gender, lower MMSE score and higher ADAS-cog score, had a high risk for the progression to AD.

INTRODUCTION

Alzheimer's disease (AD) is an illness turning out to be a major public health problem. The cause is unknown, whereas many individual risk factors for subsequent AD have been suggested, such as mild cognitive impairment (MCI) with an estimated conversion rate of 10–15% per year.[1] MCI represents the transitional stage from the cognitive changes of normal ageing to very early dementia.[2 3] Owing to this high risk for progression to AD, patients with MCI represent a target for future disease modifying therapies. However, as MCI is a heterogeneous entity characterised by differences in cognitive profile and clinical progression, the outcome for any patients with MCI is uncertain. Many patients may remain stable or even revert to a normal state, while others progress to AD. Therefore, insight is needed into the specific risk factors and biomarkers that predict progression from MCI to AD, in order to be able to identify individuals within the MCI population who are at the highest risk of developing AD in the near future. These individuals will subsequently constitute a target population for (early) intervention studies. There were also separate studies and meta-analyses indicating that apolipoprotein Eε4 (APOEε4), depression and diabetes were risk factors for the disease's progression.[4–6] However, some of the conclusions seem to be conflicting. As a result, it was necessary for us to report a large and comprehensive systematic review and meta-analysis for clinicians using an extensive search of cohort studies to identify the risk factors for progression to AD of a population with MCI.

METHODS

Search strategy

We conducted a systematic literature search of PubMed, OVID, EMBASE, the Cochrane library, the Library of Congress and EBSCO, for studies published in the period from January 1966 to March 2015. Terms we used included 'risk factors', 'Alzheimer's disease' and 'mild cognitive impairment', combined with Boolean operators as appropriate. We restricted our analysis to articles written in English. Additional studies were obtained from the reference lists of identified studies.

Study selection

Published studies were included if they fulfilled the following criteria: (1) the study had a cohort design; (2) baseline population meet the criteria for the diagnosis of MCI; (3) they assessed at least one risk factor for predicting progression from MCI to AD; (4) AD and dementia were both defined as the end points; (5) for multiple articles identified from a single study, preference was given to the publication with the longest follow-up period or the most comprehensive reporting of relevant data (the comprehensive reports mainly indicated the largest scale report among these reports about 1 study or database) and (6) they reported original data on

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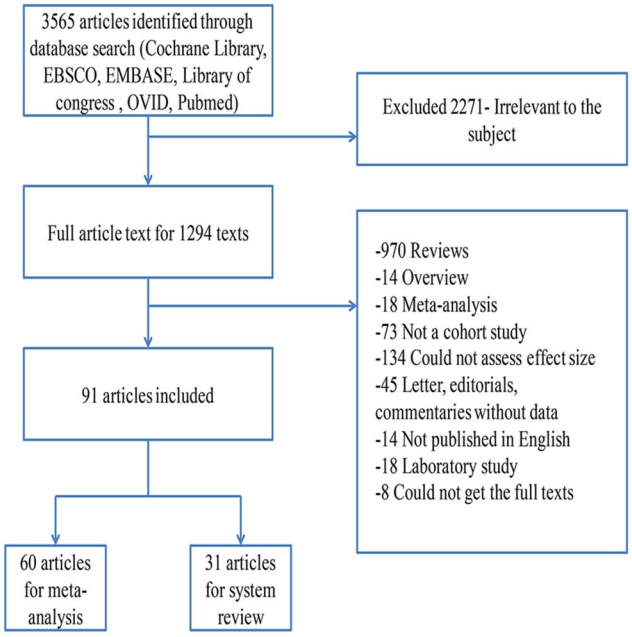

Figure 1 Flow chart of study selection.

relative risks (RRs), HRs or ORs, and 95% CI or sufficient data to calculate an effect size. We excluded review articles, editorials, commentaries, hypothesis papers, letters that reported no new data, meta-analysis and abstracts.

Data extraction and quality assessment

We extracted the following variables from each study: (1) name of the first author; (2) publication year; (3) country; (4) follow-up time in years; (5) study resource; (6) definition of MCI; (7) genders of patients; (8) mean age of patients; (9) baseline mini-mental state examination (MMSE) score; (10) number of patients at the baseline and the proportion of completing the follow-up; (11) overall incidence of dementia or AD; (12) exposure assessment and (13) effect size and 95% CIs. The discrepancies were resolved by discussion. If studies did not report RR, HR or OR, the raw data were reviewed to determine whether effect size could be calculated. In studies that reported both crude RRs and adjusted RRs, the adjusted figures were used.

The Newcastle Ottawa Scale (NOS)[7] was used to assess the quality of each study. This measure assesses aspects of methodology in observational studies related to study quality, including selection of cases, comparability of populations and

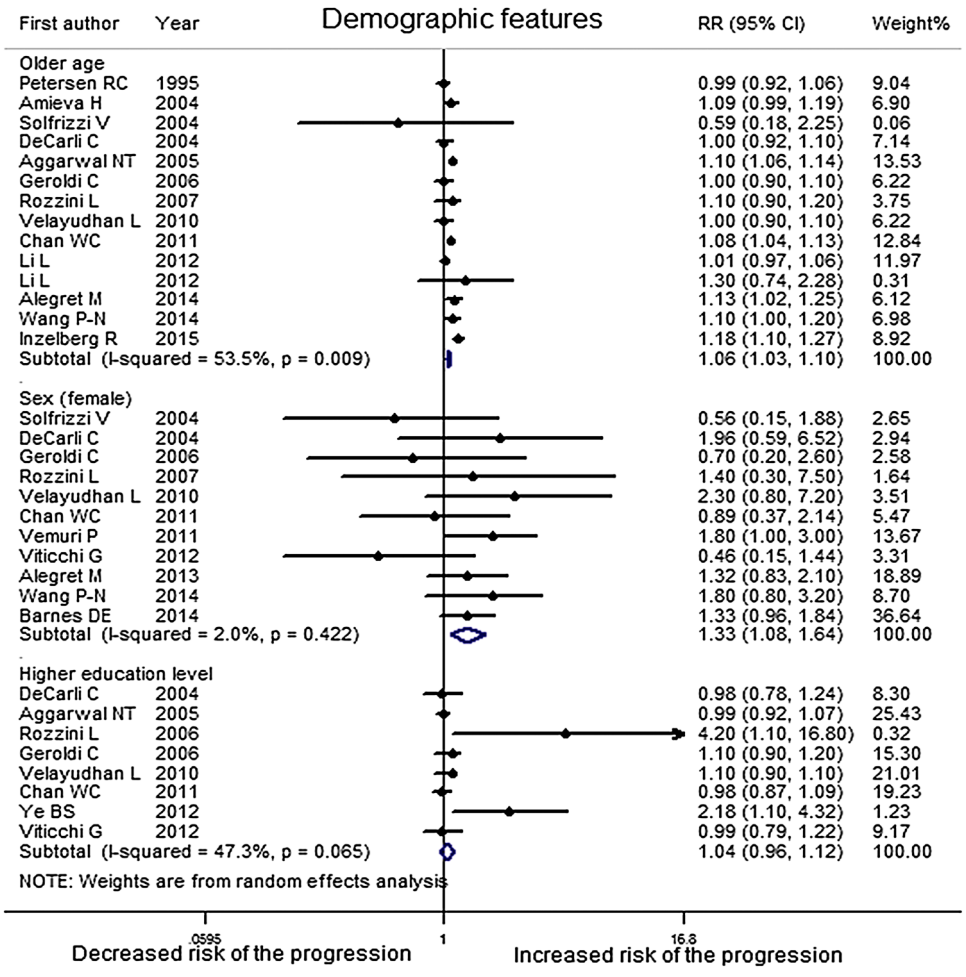

Figure 2 Forest plot shows the association between demographic features and the risk of progression from MCI to AD (AD, Alzheimer's disease; MCI, mild cognitive impairment; RR, relative risk).

ascertainment of exposure to risks. We identify 'high' quality choices with a 'star'. A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. Studies with a score equal to or higher than seven were considered to be high quality.

Statistical analysis

When studies provided more than one risk factor, we performed multivariate analysis. Otherwise, univariate analysis would be conducted. If a factor of interest was reported by three or more studies in a consistent manner, they were combined in a meta-analysis. We classified them according to different risk factors and carried out subgroup analysis among risk factors that were homogeneous. We generated a pooled effect size and 95% CI for each factor. Acquiescently, we chose a fixed effect model. Heterogeneity between studies was assessed using the I^2 statistic and, where statistically significant heterogeneity was found (I^2>50%, p<0.05), the random effects model was used to combine results.[8 9] Before that, we reviewed the primary literature and performed sensitivity analyses to examine the source of the heterogeneity. Publication bias was assessed by using the Begg's test.[10] Where data were not given in a way that could be used in the meta-analysis or where only one or two significant studies were identified for a given risk factor, the findings of these studies are only listed in Discussion section. All analyses were performed using Stata V.12.

RESULTS

Eligible studies

The literature search yielded 3565 English language articles, of which 60 were eligible for inclusion in the meta-analysis and 31 in the systematic review (s-References 1–91) (figure 1). Quality assessment showed that the NOS score of each study was not less than 7, indicating that the methodological quality was generally good (see online supplementary table S1). Full details of studies included in the meta-analysis were provided (see online supplementary tables S2 and S3). The 31 articles could not be included in the meta-analysis, as the quality scores were lower than 5. Another reason was that less than two studies had reported a result on a given factor.

Assessment of risk factors

Demographic features

There were 33 studies about demographic predictors (older age, sex (female) and high education level) in our meta-analysis.

After pooling every subgroup, older age (RR=1.06, 95% CI=1.03 to 1.1, I^2=53.3%, p=0.009) and sex (female) (RR=1.33, 95% CI=1.08 to 1.64, I^2=2.0%, p=0.422) had a high risk of the progression in random-effects models. However, high education level (RR=1.04, 95% CI=0.96 to 1.12, I^2=47.3%, p=0.065) had no large association with the progression to AD in patients with MCI (figure 2). The Begg's test did not provide strong evidence for publication bias in the 'Demographic features' group (z=0.87(continuity corrected), Pr>|z|=0.386(continuity corrected)).

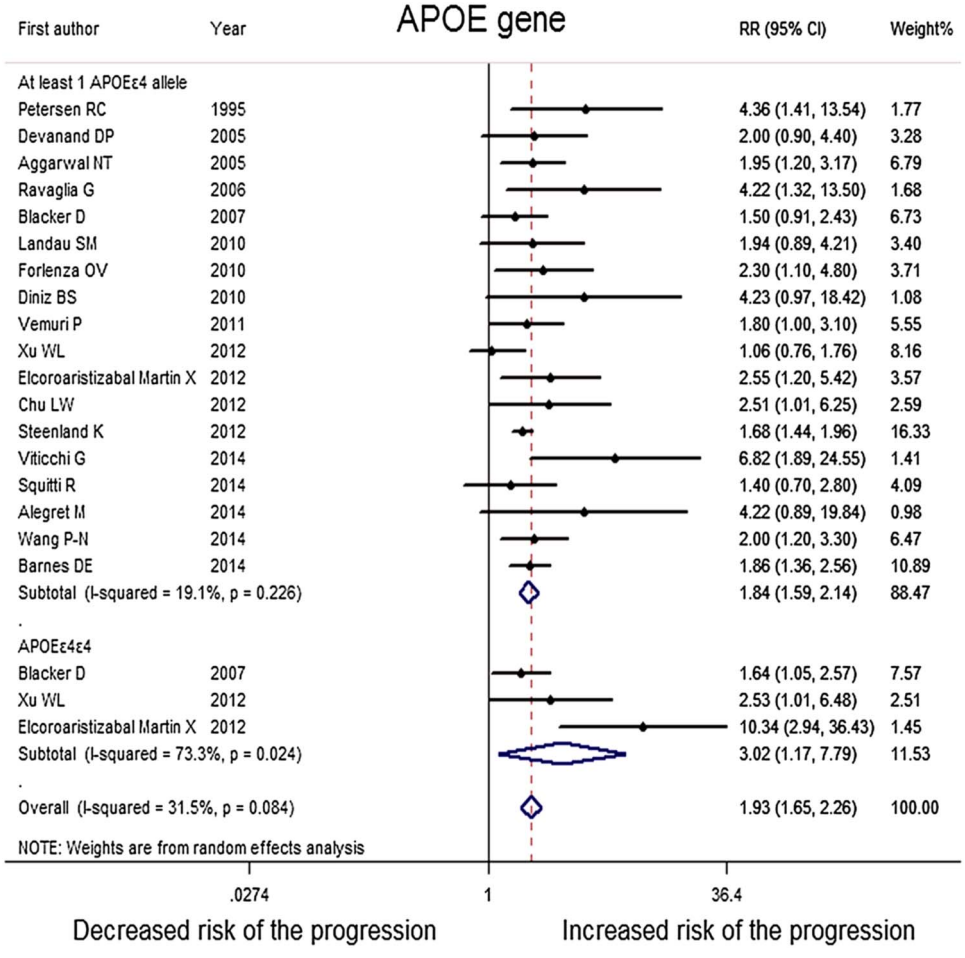

Figure 3 Forest plot shows the association between APOE gene and the risk of progression from MCI to AD (AD, Alzheimer's disease; APOE, apolipoprotein E; MCI, mild cognitive impairment; RR, relative risk).

APOE gene

Among all the studies we reviewed, risk factors on genes were all focused on *APOE*. We performed subgroup analysis between 'at least one APOEε4 allele' and 'APOEε4ε4'.

In the presence of at least one APOEε4 allele, the pooled RR for progression to AD in all studies was 1.84 (95% CI=1.59 to 2.14) with the heterogeneity across studies (I^2=19.1%, p=0.026). In addition, in the presence of APOEε4ε4, the pooled RR for the progression in all studies was 3.02 (95% CI=1.17 to 7.79) from a random-effects model as the heterogeneity across studies (I^2=73.3%, p=0.024). The overall effect size 1.93 (95% CI=1.65 to 2.26), heterogeneity (I^2=31.5%, p=0.084) and publication bias (z=0.31(continuity corrected), Pr>|z|=0.760(continuity corrected)) of the two subgroups indicating APOEε4 is a risk factor for the progression from MCI to AD (figure 3). We also conduct subgroup meta-analysis by race to 'At least 1 APOEε4 allele' factor. There was no heterogeneity between subgroup: p=0.355 (see online supplementary figure S2).

Lifestyle factors

As to lifestyle, there are seven studies reporting on the association between smoking and the risk of progression from MCI to AD. Among included studies, there was also one article about alcohol consumption, which would be discussed in the system review. After pooling these 11 studies, results showed no significant association between smoking and the risk of the progression (RR=0.98, 95% CI=0.96 to 1.01, I^2=19.5%, p=0.281). There was also no significant heterogeneity among these studies (figure 4). The Begg's test did not provide obvious publication bias in the 'Lifestyle factors' group (z=0.30(continuity corrected), Pr>|z|=0.764(continuity corrected)).

Cognitive and psychological factors

Seventeen of the included studies compared risk of progression to AD between patients with MCI with and without physiological and psychological factors (anxiety, apathy, depression). An apathy syndrome is defined as a syndrome of primary motivational loss, that is, loss of motivation not attributable to emotional distress, intellectual impairment, or diminished level of consciousness.[11] Although related to depression, apathy is a motivational disorder that can be distinguished from depression, which is characterised by feelings of sadness, hopelessness or inappropriate guilt.[12] Besides, anticipation of and preparation for future harm are central features of anxiety.

After pooling these studies, patients with MCI with anxiety (RR=1.42, 95% CI=0.57 to 3.57, I^2=86.5%, p=0.001) and apathy (RR=1.46, 95% CI=0.68 to 3.14, I^2=84.5%, p=0.000) both had no significant association with the progression to AD. However, depression (RR=1.35, 95% CI=1.05 to 1.75, I^2=76.0%, p=0.000) had a high risk of the progression in random-effects models (figure 5). The Begg's test did not provide obvious publication bias in the 'Cognitive and psychological factors' group (z=0.30(continuity corrected), Pr>|z|=0.764(continuity corrected)).

Vascular disorders

Most patients with MCI have basic diseases. In this study, we analyse seven of them. Thirty-five of the included studies reported on them (hypertension, diabetes, cerebrovascular disease, cardiovascular disease, atrial fibrillation, hypercholesterolaemia and high body mass index).

After pooling every subgroup, patients with diabetes (RR=1.52, 95% CI=1.2 to 1.91, I^2=20.0%, p=0.271) and hypertension (RR=1.18, 95% CI=1.1 to 1.27, I^2=0.0%,

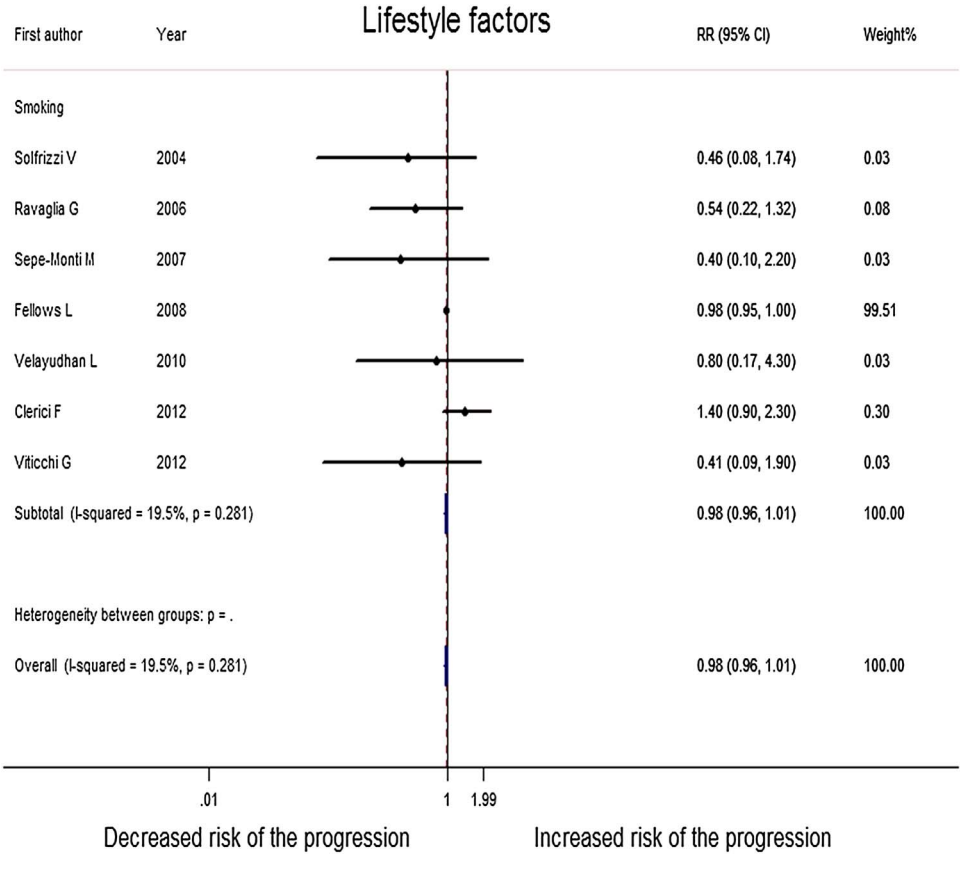

Figure 4 Forest plot shows the association between life styles factors and the risk of progression from MCI to AD (AD, Alzheimer's disease; MCI, mild cognitive impairment; RR, relative risk).

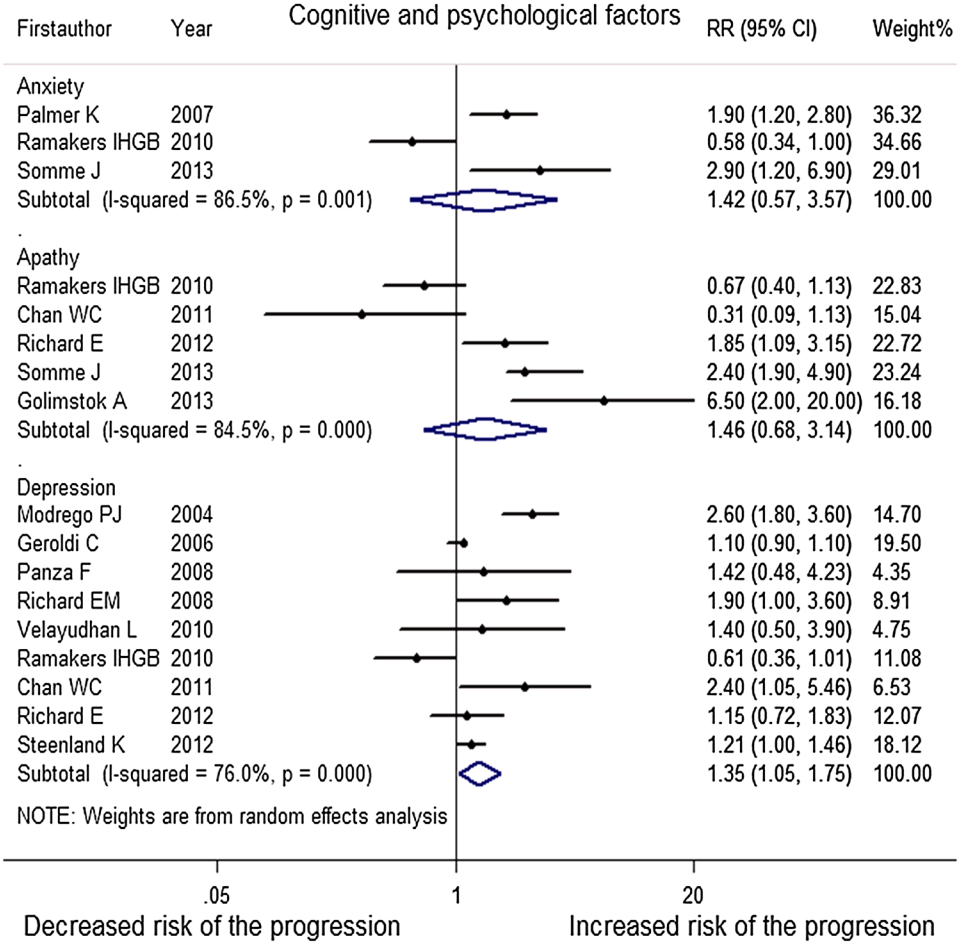

Figure 5 Forest plot shows the association between cognitive and psychological factors and the risk of progression from MCI to AD (AD, Alzheimer's disease; MCI, mild cognitive impairment; RR, relative risk).

p=0.658) have high risk for the progression. However, for cardiovascular disease (RR=0.83, 95% CI=0.55 to 1.26, I^2=0.0%, p=0.534), cerebrovascular disease (RR=1.61, 95% CI=0.94 to 2.75, I^2=31.4%, p=0.212), atrial fibrillation (RR=2.60, 95% CI=0.42 to 16.11, I^2=92.9%, p=0.000) and hypercholesterolaemia (RR=0.48, 95% CI=0.13 to 1.82, I^2=90.8%, p=0.000), they had no large association with the progression to AD in patients with MCI. High body mass index had an especially protective effect to the progression (RR=0.85, 95% CI=0.76 to 0.96, I^2=0.0%, p=0.530). Atrial fibrillation and hypercholesterolaemia had high heterogeneity; we had performed on random-effect models (figure 6). The Begg's test did not provide significant evidence for publication bias in the 'Vascular disorders' group (z=0.73(continuity corrected), Pr>|z|=0.462(continuity corrected)).

MRI markers

There were 19 studies included in meta-analysis (hippocampal atrophy, medial temporal lobe atrophy, entorhinal atrophy, white matter hyperintensity (WMH) volume and subcortical infarctions).

After pooling these studies, patients of MCI with hippocampal atrophy (RR=2.59, 95% CI=1.95 to 3.44, I^2=0.0%, p=0.964), medial temporal lobe atrophy (RR=2.11, 95% CI=1.70 to 2.63, I^2=41.7%, p=0.161), entorhinal atrophy (RR=2.03, 95% CI=1.57 to 2.62, I2=46.1%, p=0.157) and WMH volume (RR=1.03, 95% CI=1.00 to 1.07, I^2=13.1%, p=0.331), had significant higher incidence of AD than those without, in fixed-effects models. However, no obvious association was found for subcortical infarctions (RR=0.93, 95% CI=0.51 to 1.71, I^2=44.9%, p=0.163) (figure 7). The Begg's test did not provide obvious publication bias in the 'MRI markers' group (z=0.63(continuity corrected), Pr>|z|=0.533 (continuity corrected)).

Cerebrospinal fluid markers

Among various biomarkers reported to be predictors for the progression from MCI to AD, there are 10 studies on Aβ, t-τ and p-τ. However, the ratio of cerebrospinal fluid (CSF) τ and $Aβ_{1–42}$ (CSF τ/$Aβ_{1–42}$) is a significant predictor, with three studies reported on it.

The meta-analysis indicated that abnormal CSF t-τ (RR=1.86, 95% CI=1.35 to 2.55; I^2=0.0%, p=0.798), abnormal CSF p-τ (RR=2.43, 95% CI=1.70 to 3.48; I^2=0.0%, p=0.490) and abnormal CSF τ/$Aβ_{1–42}$ (RR=3.77, 95% CI=2.34 to 6.09; I^2=0.0%, p=0.993), was associated with high risk of progression from MCI to AD. However, abnormal Aβ (RR=2.21, 95% CI=0.87 to 5.63; I^2=82.6, p=0.003) had no significant association with the progression to AD in patients with MCI (figure 8). The Begg's test did not provide significant evidence for publication bias in the 'CSF markers' group (z=1.48(continuity corrected), Pr>|z|=0.139(continuity corrected)).

Neuropsychological measures

Fifteen of the included studies (lower MMSE score, higher AD assessment scale cognitive subscale (ADAS-cog) score, higher auditory verbal learning test (AVLT) total score and higher AVLT delay score) reporting on neuropsychological measures were involved in our meta-analysis.

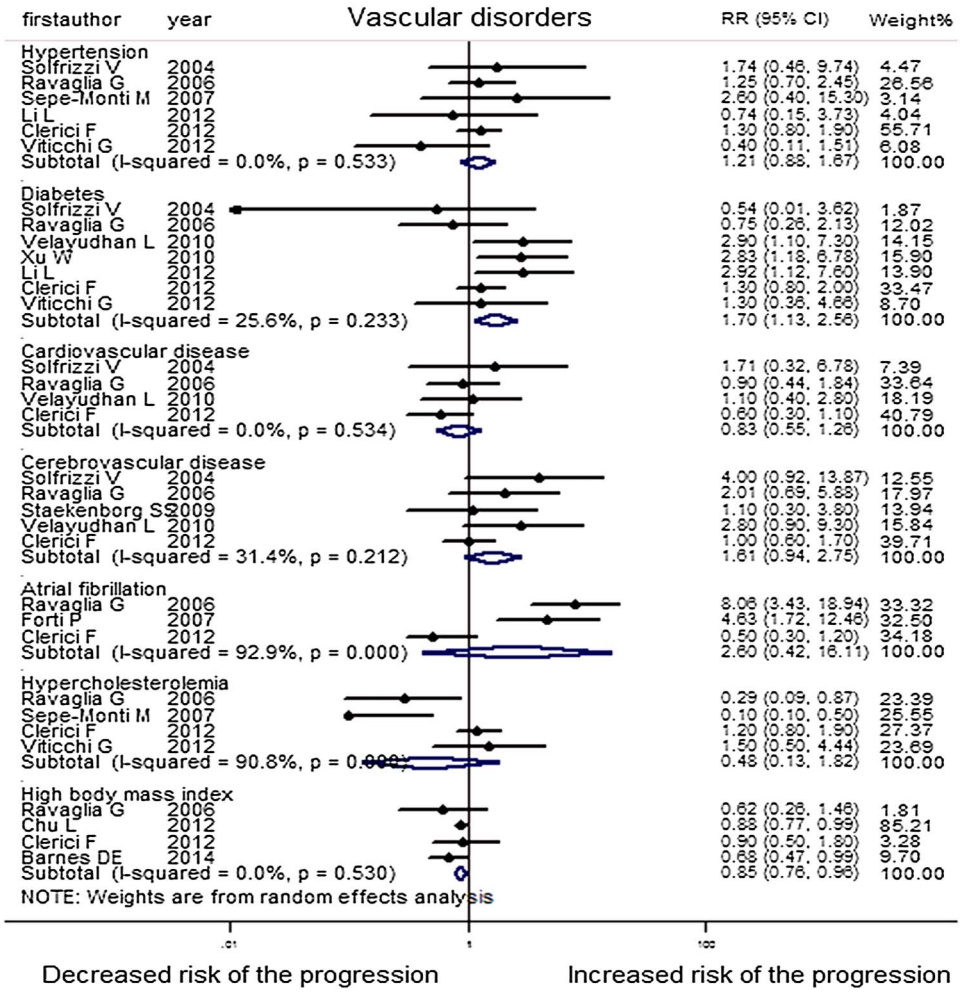

Figure 6 Forest plot shows the association between vascular disorders and the risk of progression from MCI to AD (AD, Alzheimer's disease; MCI, mild cognitive impairment; RR, relative risk).

After pooling every subgroup, lower MMSE score (RR=1.75, 95% CI=1.04 to 2.96, I^2=81.8%, p=0.004) and higher ADAS-cog score (RR=1.12, 95% CI=1.06 to 1.19, I^2=78.6%, p=0.000) had a high risk of the progression. However, higher AVLT total score (RR=1.06, 95% CI=0.74 to 1.53, I^2=93.8%, p=0.000) had no significant association with the progression to AD in patients with MCI. There was no significant heterogeneity among these studies. Higher AVLT delay score had a protective effect to the progression (RR=0.85, 95% CI=0.73 to 0.98, I^2=56.5%, p=0.130). These all had a high heterogeneity except AVLT delay, so we performed on random-effect models (see online supplementary figure S1). The Begg's test did not provide obvious evidence for publication bias in the 'neuropsychological measures' group (z=1.4(continuity corrected), Pr>|z|=0.161(continuity corrected)).

Multivariate analysis

As aforementioned, a single risk factor could significantly predict the disease progression, however, some individuals had a variety of risk factors. When studies provided more than one risk factor, we performed multivariate analysis. The results showed that combining different classes of risk factors could even more strongly predict the conversion from MCI to AD. The combination of low CSF $A\beta_{42}$ and high CSF τ levels could significantly predict the progression from MCI to AD (s-References 60, 89). It combined Aβ and τ levels as a predictor so as to improve the specificity. Another study indicated abnormal $\tau/A\beta_{1-42}$ combining with low AVLT score or medial temporal lobe atrophy improved outcome prediction (s-References 1, 12, 23).

DISCUSSION

This meta-analysis was the inclusion of cohort studies from six online database searches, covering published literature from nearly 50 years. We evaluated 28 probable risk factors for predicting progression from MCI to AD. In order to ensure the quality, we carefully developed the inclusion criteria for studies and conducted strict quality evaluation. This piece of work involves extensive analysis and hopefully will provide valuable insights and inspiration to clinicians.

The following are the major points revealed from this meta-analysis: (1) the presence of at least one APOEε4 allele, APOEε4ε4 allele, abnormal CSF p-τ, t-τ and $\tau/A\beta_{1-42}$, hippocampal and media temporal lobe atrophy, entorhinal atrophy, WMH volume, depression, diabetes, hypertension, older age and female gender, lower MMSE score and higher ADAS-cog score all had high risk for the progression from MCI to AD. (2) Subcortical infarctions, anxiety, apathy, smoking, cardiovascular disease, cerebrovascular disease, atrial fibrillation, hypercholesterolaemia, higher education level and higher AVLT total had no significant risk to the progression. (3) High body mass index and higher AVLT delay had a protective effect to the progression.

Older and female patients with MCI were more likely to progress to AD; however, the impact of education level on the progression risk seems to be controversial. As to a variety of

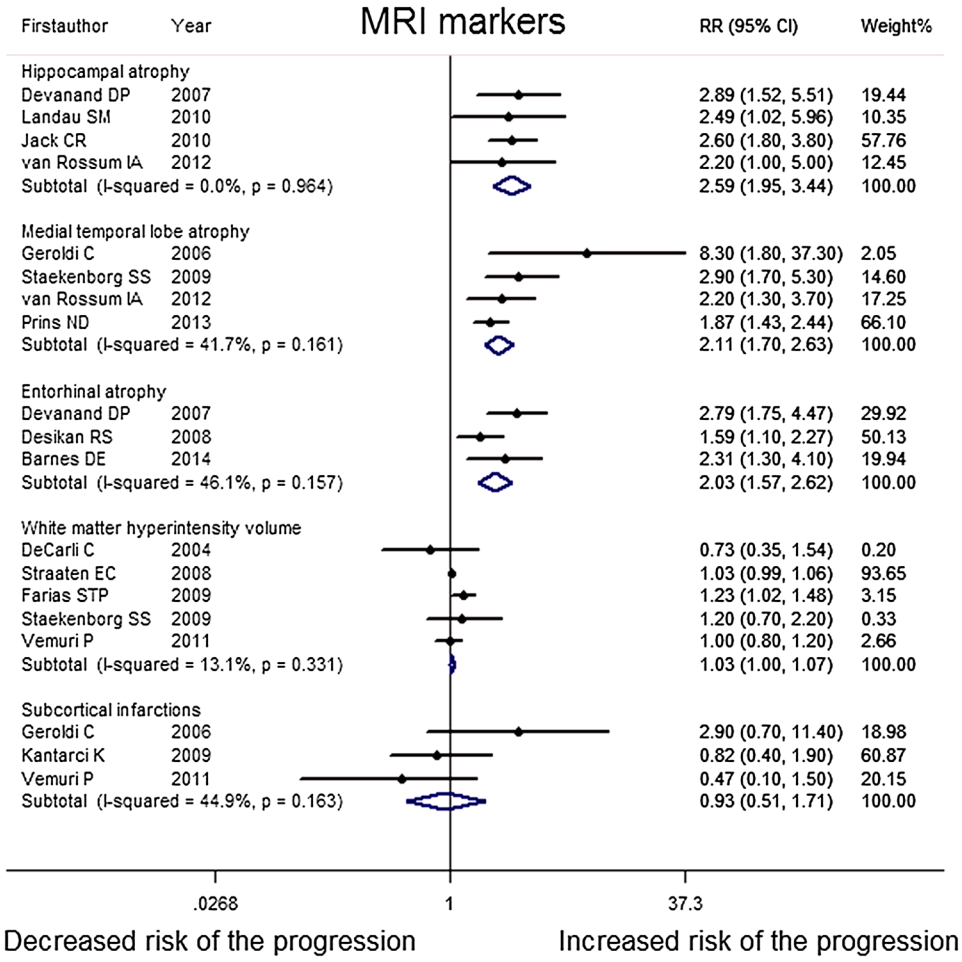

Figure 7 Forest plot shows the association between MRI markers and the risk of progression from MCI to AD (AD, Alzheimer's disease; MCI, mild cognitive impairment; RR, relative risk).

scoring criteria, classical criteria such as MMSE, ADAS and AVLT had a considerable predictive value. Besides, lower scores in "memory impairment screen plus" and "word list recall of verbal memory and orientation" also contributed to the prediction of conversion (s-Reference 64, 70).

The APOEε4 allele is the strongest known genetic risk factor for AD. It is supposed to alter β-amyloid processing or to modify the response to AD pathology and could be a new therapeutic target for the treatment of AD. Other than our findings, a recent meta-analysis published at 2011 indicated the positive predictive value of APOEε4 allele for progression from MCI to AD-type dementia.[5] However, their effect sizes were OR, sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios. Moreover, one study indicated that APOE is a significant predictor of the conversion to AD among patients with MCI (s-Reference 10). Based on all these studies, there is convincing evidence to suggest that APOEε4 has significant risk for the progression from MCI to AD.

As to lifestyle, smoking as well as alcohol consumption and insomnia had no obvious association with the risk of the disease progression (s-References 42, 51, 56). However, higher adherence to the Mediterranean diet is associated with a reduced risk for MCI conversion to AD (s-Reference 71). Patients with four neuropsychiatric symptoms (NPS) had nearly 2.5 times the odds of developing dementia at follow-up than patients with 0–3 NPS (s-Reference 65). A recent meta-analysis of 12 studies published in 2012 showed that depression was a major risk factor for incidence of dementia (including AD, vascular dementia and any dementia) and MCI.[6] It also included cohort studies, but focused on subjects without dementia or MCI at baseline. As depression could be managed through psychotherapy, medication, electroconvulsive treatment, and so on,[13] our finding implied that depression treatment might be applied to prevent or delay the occurrence and development of AD in patients with MCI.

Diabetes mellitus is associated with changes in cognition. Several large longitudinal population-based studies have shown that elderly people with type 2 diabetes had an increasing rate of cognitive decline.[14] A quantitative meta-analysis showed that diabetes was a risk factor for incident dementia (including AD, vascular dementia and any dementia) and MCI.[4] Our analysis shows that diabetes was the only independent predictor of conversion from MCI to dementia among all vascular risk factors studied. Moreover, among those with MCI, baseline levels of lower extremity motor performance, parkinsonian gait and bradykinesia were inversely related to risk of AD, even after controlling for clinical stroke (s-Reference 66). Besides, intracranial arterial stenosis and olfactory identification deficits, particularly with lack of awareness of olfactory deficits, increased the risk of developing AD dementia after MCI (s-Reference 62, 80). Hypertension had positive association with the risk of the progression and the use of antihypertensive medications was protective (s-Reference 76). Furthermore, a recent study showed that patients with cardiovascular risk factors had higher conversion rate to AD (s-Reference 85).

MRI is an important means to diagnose AD. The medial temporal lobe, which includes the hippocampus and parahippocampal gyrus (the latter includes the entorhinal cortex), atrophies early in AD.[15] In patients with AD, hippocampal volume is smaller than in controls and is associated with greater risk of

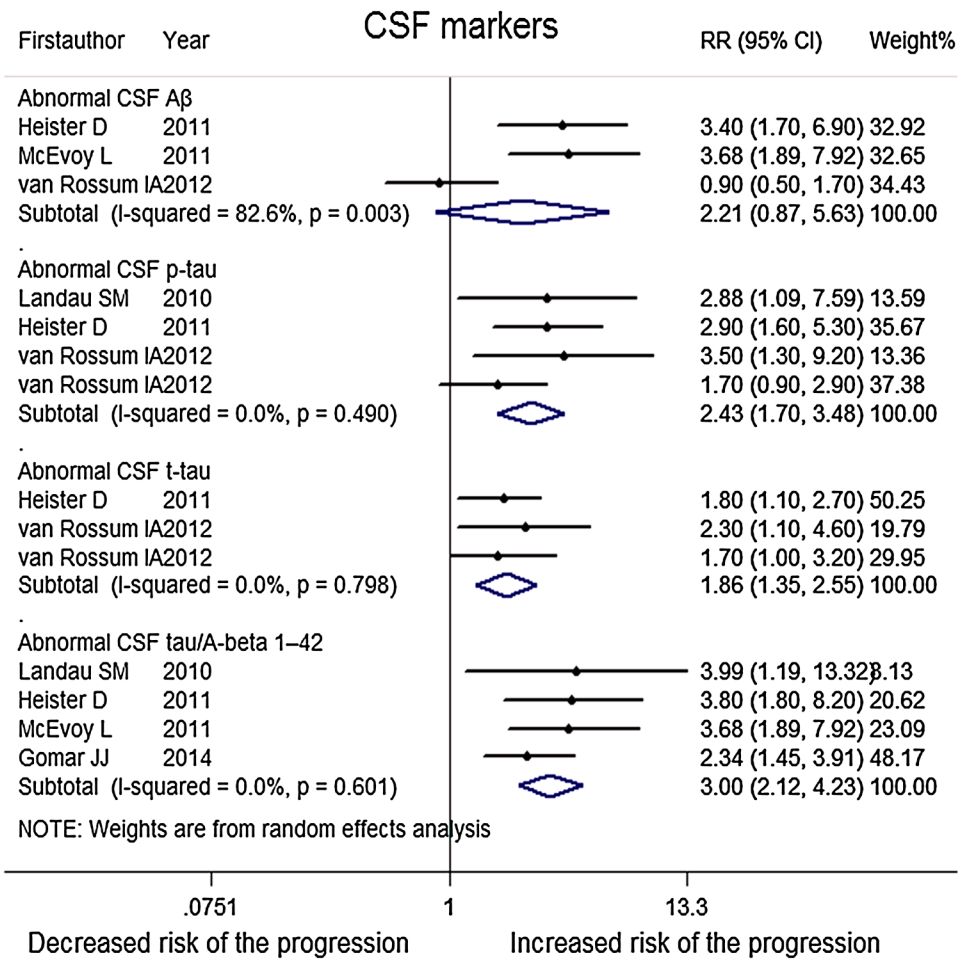

Figure 8 Forest plot shows the association between CSF markers and the risk of progression from MCI to AD (AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; RR, relative risk).

dementia.[16] Similarly, entorhinal cortex volume is smaller in patients with AD compared with controls.[17] As expected, they all showed significant value in predicting the progression from MCI to AD in the current meta-analysis. Another study indicated that converters showed greater atrophy in the hippocampus, predominantly in the CA1 region and subiculum, and in the entorhinal cortex, especially in the anterior–inferior pole bilaterally (s-Reference 79). Compared with our findings, they narrowed the extension and provided more accurate positioning. Infarctions and WMHs have been associated with an increased risk of cognitive decline in normal people.[18 19] However, in our meta-analysis, WMH volume shows slight value in predicting the progression and subcortical infarctions show no significant association with the risk. Moreover, among patients with MCI, both greater ventricular volume and whole brain annual per cent volume change and age-related white matter changes in the basal ganglia (both sides) increased the risk of conversion to AD (s-Reference 59, 81). Higher apparent hippocampal diffusion coefficient values and lower hippocampal W-scores in people with amnestic MCI at baseline are both associated with a higher RR of progression to AD in the future (s-Reference 75).

Concentrations of t-τ and p-τ can be measured in CSF and correlate with the presence of neurofibrillary tangles.[20 21] In our study, increased CSF level of t-τ and p-τ were associated with an increased risk of progression to AD in participants with MCI, and RRs were 1.86 and 2.43, respectively. Besides, the concentration of $A\beta_{1-42}$ in CSF correlates with the presence of amyloid plaques in the brain.[20] However, Aβ in CSF did not show any associations with the progression. As it showed high heterogeneity, we reviewed the primary literature and performed sensitivity analyses to analyse the source of the heterogeneity. It showed that van Rossum's study using heterogeneity as its effect size described the progression from MCI to dementia but not AD in the other two studies. Whether abnormal Aβ in CSF could predict the progression from MCI to AD still needs further exploration. Moreover, many other biomarkers were also indicated to be predictors of the progression aside from Aβ and τ. For example, having a low baseline serum leptin level predicts an increased risk of progression to AD (s-Reference 84). However, the serum clustering level is not a predictor of progression to AD (s-Reference 7). Furthermore, patients with hyperfibrinogenaemia, a low level of cystatin C and elevated coated-platelet levels in the plasma are associated with increased risk for progression to AD (s-Reference 73, 86, 87).

Limitations of this meta-analysis must be considered. We did not hand search journals and made no attempt to identify unpublished studies. We restricted our search to articles written in English and to cohort studies and therefore some studies must have been missed. During the past five decades (from 1966 to 2014), the diagnostic criteria for MCI and AD have changed, and the various MCI subtypes had different risk of cognitive deterioration, also, we cannot obtain all the information about the typology of MCI; these factors may influence the final results. Owing to the large number of studies, we cannot fully unify the exposure assessment measures and the adjustments. Statistically significant heterogeneity was found in 10 of the meta-analyses performed. In two of these, there was

moderate heterogeneity (I^2=50–75%), and in eight there was high heterogeneity (I^2>75%). This is because of the differences between individual studies in, for example, study population characteristics, study resource, mean years of follow-ups, exposure measurements and whether crude or adjusted risk estimates were reported. For this reason, we performed on a random-effects model.

In conclusion, this is a comprehensive systematic review and meta-analysis taking into account all risk factors for the progression from MCI to AD. The numerous proposed risks may help to develop new therapy approaches and conduct earlier intervention in order to prevent or delay the occurrence and development of AD in patients with MCI. However, the treatments to these risk factors and the progression rates to AD in patients with MCI should be further confirmed by using large sample sizes and high-quality studies.

Contributors LT and J-TY conceived the study. J-QL, H-FW, LT, WX, Q-FZ, TJ, M-ST and JW selected reports and extracted the data. J-QL and H-FW analysed and interpreted the data. J-QL and J-TY wrote the first draft of the manuscript. All the authors critically revised the manuscript for intellectual content and approved the final version. LT and J-TY are guarantors.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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Figure s1 Forest plot shows the association between neuropsychological measures and the risk of progression from MCI to AD. RR=relative risk CI=confidence interval

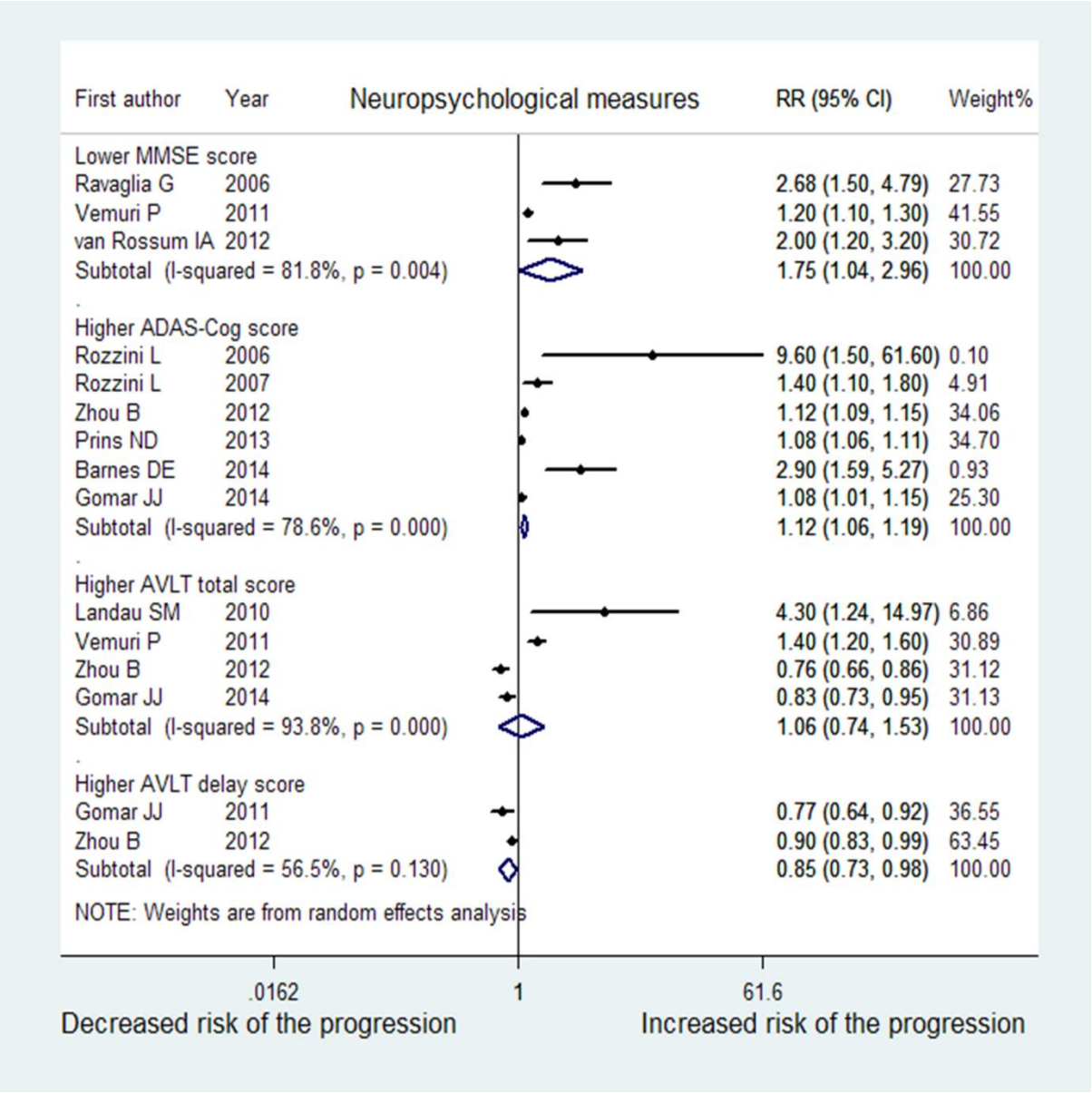

Figure s2 Forest plot shows the association between “At least 1 APOEe4 allele” factor and the risk of progression from MCI to AD with subgroup meta-analysis by race. RR=relative risk CI=confidence interval

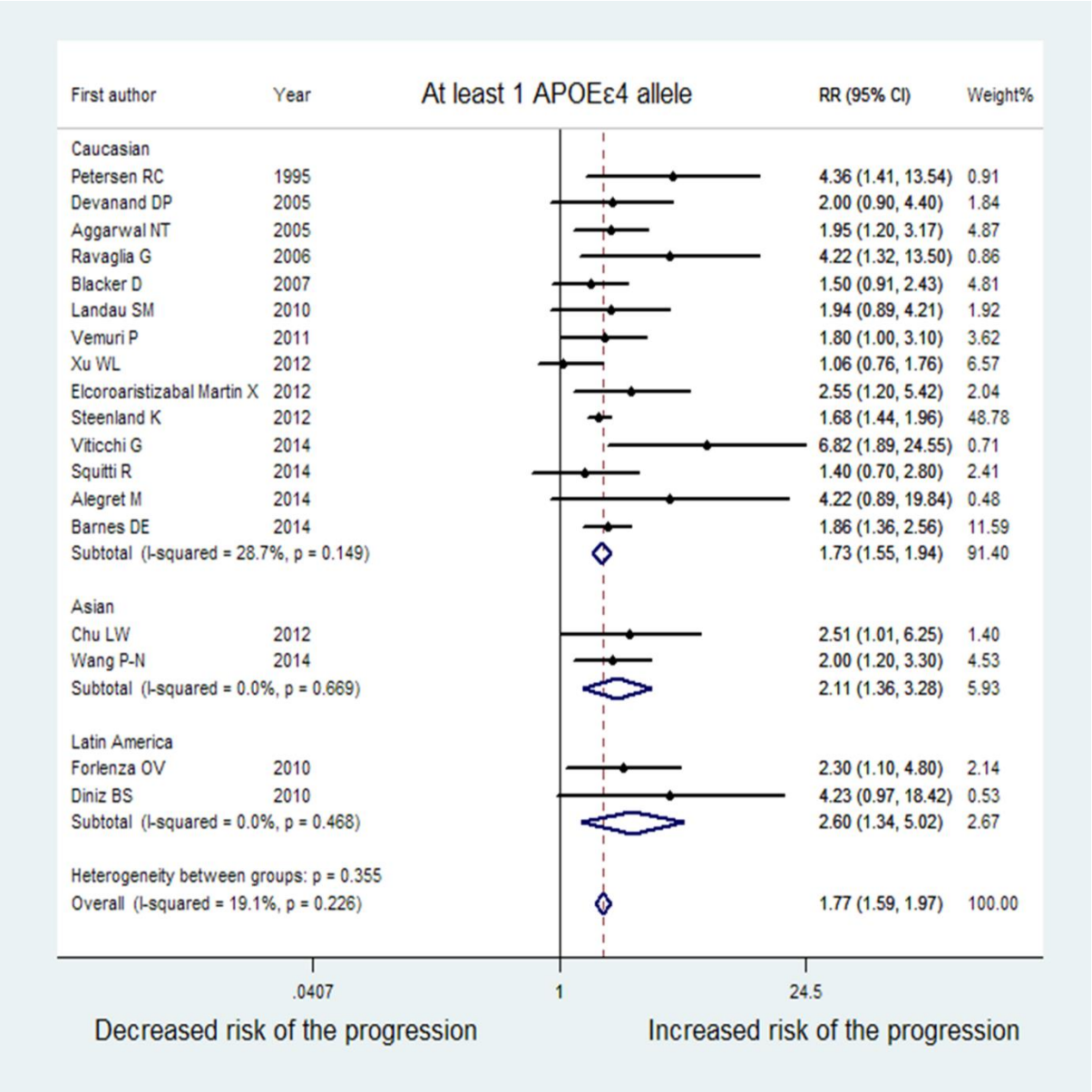

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Table s-1: Quality Indicators From Newcastle-Ottawa Scale40*

e-Ref	Year	First author	1	2	3	4	5A	5B	6	7	8	Total score
1	2012	van Rossum IAMD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
2	2013	Prins ND	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
3	2012	Xu WL	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
4	2007	Blacker D	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
5	2012	Elcoroaristizabal Martin X	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
6	2014	Viticchi G	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	8
7	2014	Squitti R	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
8	2010	Landau SM	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	8
9	2005	Devanand DP	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
10	2011	Gomar JJ	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
11	2012	Chu LW	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	7
12	2011	Heister D	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
13	2010	Forlenza OV	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
14	2006	Ravaglia G	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8

15	2010	Diniz BS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8
16	1995	Petersen RC	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	7
17	2007	Forti P	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
18	2007	Sepe-Monti M	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
19	2007	Devanand DP	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
20	2010	Jack CR	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
21	2009	Kantarci K	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
22	2013	Somme J	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
23	2011	McEvoy L	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
24	2012	Chu L	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
25	2007	Palmer K	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
26	2012	Ye BS	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
27	2009	Farias STP	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
28	2012	Zhou B	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
29	2008	Desikan RS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
30	2004	Amieva H	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8

31	2008	Fellows L	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
32	2006	Rozzini L	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
33	2005	Aggarwal NT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
34	2012	Li L	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
35	2014	Alegret M	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
36	2007	Rozzini L	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
37	2014	Wang P-N	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
38	2011	Chan WC	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
39	2004	Solfrizzi V	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
40	2004	DeCarli C	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	8
41	2006	Geroldi C	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8
42	2010	Velayudhan L	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
43	2012	van Rossum IA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
44	2009	Staekenborg SS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8
45	2011	Vemuri P	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7
46	2012	Richard E	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9

47	2008	Straaten EC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
48	2010	Xu W	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
49	2012	Clerici F	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
50	2012	Viticchi G	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8
51	2014	Barnes DE	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
52	2008	Panza F	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
53	2004	Modrego PJ	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
54	2008	Richard EM	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
55	2012	Steenland K	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	8
56	2010	Ramakers IHGB	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
57	2013	Golimstok A	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
58	2014	Gomar JJ	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
90	2014	Ma F	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
91	2015	Inzelberg R	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9

*1 indicates exposed cohort truly representative; 2, nonexposed cohort drawn from the same community; 3, ascertainment of exposure; 4, outcome of interest not present at start; 5A, cohorts comparable on basis of age; 5B, cohorts comparable on other factor(s); 6, quality of outcome assessment; 7, follow-up long enough for

outcomes to occur; and 8, complete accounting for cohorts.

Table s-2: Characteristics of patients included in meta-analysis

First author	Year	Country	Resource	MCI definition	Sample size, baseline (% FU)	Female (%)	Mean age (years)	Mean education (years)	MMSE score	Exposure	e-Ref
Petersen RC	1995	USA	Mayo Clinic Alzheimer's Disease Center/Alzheimer's Disease Patient Registry	MCI	66(100)	48(73)	79.8	13.9	26.24	Older age	16
Amieva H	2004	France	–	MCI	90(-)	40(44)	70.2	–	27.7	Older age	30
Aggarwal NT	2005	USA	The Religious Orders Study	MCI	184(98)	123(67.9)	78.7	17.8	27.4	Older age	33
Li L	2012	China	Inpatients in theDepartment of Neurology of Daping Hospital in the city of Chongqing during March–September 2008	MCI	257(96)	111 (43.19)	70.05	–	25.17	Older age	34
Alegret M	2014	Spain	–	aMCI	42(93)	26(66.67)	76.52	–	25.77	Older age	35
Rozzini L	2007	Italy	Center of Neurodegenerative and Aging related Disease of the Neurological Clinic, University of Study, Brescia, Italy	aMCI	119(100)	74(62.2)	70.6	7.8	26.9	Older age	36

Wang P-N	2014	Taiwan	The memory clinic of Taipei Veterans General Hospital	aMCI	304（75）	124(40.79)	75.3	11.1	26.8	Older age	37
Chan WC	2011	Hong Kong	two community samples, a‘random recruit’sample and a‘volunteer’sample, of ethnic Chinese who were 60 or above	MCI	321(100)	225(70)	77.3	2.9	24.3	Older age	38
Solfrizzi V	2004	Italy	the Italian Longitudinal Study on Aging(ILSA)	MCI	121(100)	61 (50.4)	80.7	2.2	21.5	Older age	39
DeCarli C	2004	USA	A prospective longitudinal research project examining the role of CVD and AD on cognition	MCI	52(75)	15(29)	72.8	14.8	–	Older age	40
Geroldi C	2006	Italy	Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Scientific Institute for Research and Care Brescia, Italy	MCI	52（100）	29（56）	70	7.2	27.2	Older age	41
Velayudhan L	2010	UK	local primary care practices in south London	MCI	103(59)	66 (64)	79.4	10.6	26.3	Older age	42
Li L	2012	Italy	dementia outpatient service	MCI	117(100)	57(48.7)	75.7	7.4	27.02	Older age	50

Inzelberg R	2015	Israel	An Arab community of 81400 inhabitants located in northern Israel	MCI	297(78)	153(78)	73	–	–	Older age	91
Alegret M	2013	Netherlands	at a total of 177 centers in 16 countries	MCI	426(100)	233(55)	71	–	–	Sex (female)	2
Rozzini L	2007	Italy	Center of Neurodegenerative and Aging related Disease of the Neurological Clinic, University of Study, Brescia, Italy	aMCI	119(100)	74(62.2)	70.6	7.8	26.9	Sex (female)	36
Wang P-N	2014	Taiwan	The memory clinic of Taipei Veterans General Hospital	aMCI	304（75）	124(40.79)	75.3	11.1	26.8	Sex (female)	37
Chan WC	2011	Hong Kong	two community samples, a‘random recruit’sample and a‘volunteer’sample, of ethnic Chinese who were 60 or above	MCI	321(100)	225(70)	77.3	2.9	24.3	Sex (female)	38
Solfrizzi V	2004	Italy	the Italian Longitudinal Study on Aging(ILSA)	MCI	121(100)	61 (50.4)	80.7	2.2	21.5	Sex (female)	39
DeCarli C	2004	USA	A prospective longitudinal research project examining the role of CVD and AD on cognition	MCI	52(75)	15(29)	72.8	14.8	–	Sex (female)	40

Geroldi C	2006	Italy	Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Scientific Institute for Research and Care Brescia, Italy	MCI	52（100）	29（56）	70	7.2	27.2	Sex (female)	41
Velayudhan L	2010	UK	local primary care practices in south London	MCI	103(59)	66 (64)	79.4	10.6	26.3	Sex (female)	42
Vemuri P	2011	USA	Mayo Clinic AD Research Center	aMCI	296(42)	51 (41.5)	77	15	27	Sex (female)	45
Viticchi G	2012	Italy	dementia outpatient service	MCI	117(100)	57(48.7)	75.7	7.4	27.02	Sex (female)	50
Barnes DE	2014	USA	Alzheimer’s Disease Neuroimaging Initiative 1	aMCI	382	137 (36)	75	–	–	Sex (female)	51
Ye BS	2012	Republic of Korea	a part of the Clinical Research Center for Dementia of South Korea (CREDOS) study, which is a multicenter hospital-based registry study.	aMCI	249	134 (53.8)	71.3	9.9	26.4	Higher education level	26
Rozzini L	2006	Italy	Center of Neurodegenerative and Aging related Disease of the Neurological Clinic, University of Brescia, Italy	aMCI	74	54(73)	71.6	7.6	26.4	Higher education level	32

Aggarwal NT	2005	USA	The Religious Orders Study	MCI	184(98)	123(67.9)	78.7	17.8	27.4	Higher level	education	33
Chan WC	2011	Hong Kong	two community samples, a‘random recruit’sample and a‘volunteer’sample, of ethnic Chinese who were 60 or above	MCI	321(100)	225(70)	77.3	2.9	24.3	Higher level	education	38
DeCarli C	2004	USA	A prospective longitudinal research project examining the role of CVD and AD on cognition	MCI	52(75)	15(29)	72.8	14.8	–	Higher level	education	40
Geroldi C	2006	Italy	Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Scientific Institute for Research and Care Brescia, Italy	MCI	52（100）	29（56）	70	7.2	27.2	Higher level	education	41
Velayudhan L	2010	UK	local primary care practices in south London	MCI	103(59)	66 (64)	79.4	10.6	26.3	Higher level	education	42
Viticchi G	2012	Italy	dementia outpatient service	MCI	117(100)	57(48.7)	75.7	7.4	27.02	Higher level	education	50

Xu WL	2012	Sweden	Kungsholmen project	MCI	233(91)	71.67	–	–	–	At least 1 APOE ε4 allele	3
Blacker D	2007	USA	Community volunteer-based sample examined at a medical institution	MCI	235(98)	56.6	72.9	15.41	29.45	At least 1 APOE ε4 allele	4
Elcoroaristizabal Martin X	2012	Spain	Neurology Departments of several hospitals	aMCI	79(100)	51.9	72.15	–	26.48	At least 1 APOE ε4 allele	5
Viticchi G	2014	Italy	consecutive subjucts referred to dementia outpatient services by general practitioners	aMCI	75(74)	65.33	74.43	8.16	25.85	At least 1 APOE ε4 allele	6
Squitti R	2014	Italy	Department of Neuroscience of the Fate benefratelli Hospital, Isola Tiberina, Rome, and at the Memory Clinic of the IRCCS Istituto Centro San Giovanni di Dio, Fatebenefratelli, Brescia, Italy	MCI	141(91)	47	70.8	–	27.2	At least 1 APOE ε4 allele	7

Landau SM	2010	USA	Alzheimer's Disease Neuroimaging Initiative	MCI	400(21)	29(34.12)	78.1	16.3	27	At least 1 APOE ε 4 allele	8
Devanand DP	2005	USA	Memory disorders outpatient clinic	MCI	136(84)	55.9	67.1	15.1	27.6	At least 1 APOE ε 4 allele	9
Chu LW	2012	Hong Kong	Ambulatory setting	aMCI	243(100)	–	–	–	–	At least 1 APOE ε 4 allele	11
Forlenza OV	2010	Brazil	Institute of Psychiatry, Faculty of Medicine, University of Sao Paulo, Brazil	MCI	71(94)	71.8	70.5	10	27	At least 1 APOE ε 4 allele	13
Ravaglia G	2006	Italy	Center for Physiopathology of Aging, University of Bologna	MCI	165(59)	81(51)	76	–	26.3	At least 1 APOE ε 4 allele	14
Diniz BS	2010	Brazil	A memory clinic at the Institute of Psychiatry, Faculty of Medicine, University of Sao Paulo, Brazil	MCI	72(93)	72.2	70.5	10.1	27	At least 1 APOE ε 4 allele	15

Petersen RC	1995	USA	Mayo Clinic Alzheimer's Disease Center/Alzheimer's Disease Patient Registry	MCI	66(100)	48(73)	79.8	13.9	26.24	At least 1 APOE ε4 allele	16
Aggarwal NT	2005	USA	The Religious Orders Study	MCI	184(98)	123(67.9)	78.7	17.8	27.4	At least 1 APOE ε4 allele	33
Alegret M	2014	Spain	–	aMCI	42(93)	26(66.67)	76.52	–	25.77	At least 1 APOE ε4 allele	35
Wang P-N	2014	Taiwan	The memory clinic of Taipei Veterans General Hospital	aMCI	304（75）	124(40.79)	75.3	11.1	26.8	At least 1 APOE ε4 allele	37
Vemuri P	2011	USA	the Mayo Clinic AD Research Center(ADRC)/AD Patient Registry (ADPR)	MCI	296(42)	51 (41.5)	77	15	27	At least 1 APOE ε4 allele	45
Barnes DE	2014	USA	Alzheimer’s Disease Neuroimaging Initiative 1	aMCI	382(100)	137 (36)	75	–	–	At least 1 APOE ε4 allele	51
Steenland K	2012	USA	30 Alzheimer’s Disease Centers in the Unites States	MCI	3010（83）	1552（51.6）	74	–	27.2	At least 1 APOE ε4 allele	55
Xu WL	2012	Sweden	Kungsholmen project	MCI	233(91)	71.67	–	–	–	APOE ε4 ε4	3
Blacker D	2007	USA	Community volunteer-based sample examined at a medical institution	MCI	235(98)	56.6	72.9	15.41	29.45	APOE ε4 ε4	4

Elcoroaristizabal Martin X	2012	Spain	Neurology Departments of several hospitals	aMCI	79(100)	51.9	72.15	–	26.48	APOE ε 4 ε 4	5
Ravaglia G	2006	Italy	Center for Physiopathology of Aging, University of Bologna	MCI	165(59)	81(51)	76	–	26.3	Smoking	14
Sepe-Monti M	2007	Italy	memory clinic of the Department of Neurological Sciences of the University of Rome 'La Sapienza'	aMCI	21(100)	13(62)	72.6	10.1	26.9	Smoking	18
Fellows L	2008	Canada	The Jewish General Hospital/McGill University Memory Clinic over a five year period	aMCI	90(100)	45(50)	73.7	10.7	27.5	Smoking	31
Solfrizzi V	2004	Italy	the Italian Longitudinal Study on Aging(ILSA)	MCI	121(100)	61 (50.4)	80.7	2.2	21.5	Smoking	39
Velayudhan L	2010	UK	local primary care practices in south London	MCI	103(59)	66 (64)	79.4	10.6	26.3	Smoking	42

Clerici F	2012	Sweden	A memory clinic (the Center for Research and Treatment of Cognitive Dysfunctions of the University of Milan)	MCI	257(95)	143 (58)	74.1	–	25.7	Smoking	49
Viticchi G	2012	Italy	dementia outpatient service	MCI	117(100)	57(48.7)	75.7	7.4	27.02	Smoking	50
Somme J	2013	Spain	–	MCI	143(100)	–	–	–	–	Anxiety	22
Palmer K	2007	Sweden	population-based Kungsholmen Project, Stockholm, Sweden	MCI	47(91)	18(39.2)	84	–	–	Anxiety	25
Ramakers IHGB	2010	Netherlands	Maastricht Memory Clinic	MCI	263(87)	116(44)	66.9	–	27.6	Anxiety	56
Somme J	2013	Spain	–	MCI	143(100)	–	–	–	–	Apathy	22
Chan WC	2011	Hong Kong	two community samples, a‘random recruit’sample and a‘volunteer’sample, of ethnic Chinese who were 60 or above	MCI	321(100)	225(70)	77.3	2.9	24.3	Apathy	38
Richard E	2012	Netherlands	Alzheimer’s Disease Neuroimaging Initiative (ADNI) database	MCI	397(100)	256(64)	74.8	15.69	27.01	Apathy	46

Ramakers IHGB	2010	Netherlands	Maastricht Memory Clinic	MCI	263(87)	116(44)	66.9	–	27.6	Apathy	56
Golimstok A	2013	Argentina	–	MCI	492(100)	315(64)	71	–	–	Apathy	57
Chan WC	2011	Hong Kong	two community samples, a‘random recruit’sample and a‘volunteer’sample, of ethnic Chinese who were 60 or above	MCI	321(100)	225(70)	77.3	2.9	24.3	Depression	38
Geroldi C	2006	Italy	Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Scientific Institute for Research and Care Brescia, Italy	MCI	52（100）	29（56）	70	7.2	27.2	Depression	41
Velayudhan L	2010	UK	local primary care practices in south London	MCI	103(59)	66 (64)	79.4	10.6	26.3	Depression	42
Richard E	2012	Netherlands	Alzheimer’s Disease Neuroimaging Initiative (ADNI) database	MCI	397(100)	256(64)	74.8	15.69	27.01	Depression	46
Panza F	2008	Italy	The electoral rolls of eight Italian municipalities	MCI	139(87)	61(50)	80.6	2.2	21.4	Depression	52

Modrego PJ	2004	Spain	From the community by family physicians and the Psychiatry Unit and other specialized units	MCI	114(93)	72(63)	72.8	–	27.8	Depression	53
Richard EM	2008	Italy	Random sampling of healthy Medicare eligible persons older than 65 years in several low-income neighborhoods with a high proportion of Hispanics in NorthernManhattan	MCI	320(100)	240(75)	77.2	9.8	–	Depression	54
Steenland K	2012	USA	30 Alzheimer’s Disease Centers in the Unites States	MCI	3010（83）	1552（51.6）	74	–	27.2	Depression	55
Ramakers IHGB	2010	Netherlands	Maastricht Memory Clinic	MCI	263(87)	116(44)	66.9	–	27.6	Depression	56
Ravaglia G	2006	Italy	Center for Physiopathology of Aging, University of Bologna	MCI	165(59)	81(51)	76	–	26.3	Hypertension	14
Sepe-Monti M	2007	Italy	memory clinic of the Department of Neurological Sciences of the University of Rome 'La Sapienza'	aMCI	21(100)	13(62)	72.6	10.1	26.9	Hypertension	18

Li L	2012	China	Inpatients in theDepartment of Neurology of Daping Hospital in the city of Chongqing during March–September 2008	MCI	257(96)	111 (43.19)	70.05	–	25.17	Hypertension	34
Solfrizzi V	2004	Italy	the Italian Longitudinal Study on Aging(ILSA)	MCI	121(100)	61 (50.4)	80.7	2.2	21.5	Hypertension	39
Clerici F	2012	Sweden	A memory clinic (the Center for Research and Treatment of Cognitive Dysfunctions of the University of Milan)	MCI	257(95)	143 (58)	74.1	–	25.7	Hypertension	49
Viticchi G	2012	Italy	dementia outpatient service	MCI	117(100)	57(48.7)	75.7	7.4	27.02	Hypertension	50
Inzelberg R	2015	Israel	An Arab community of 81400 inhabitants located in northern Israel	MCI	297(78)	153(78)	73	–	–	Hypertension	91
Ravaglia G	2006	Italy	Center for Physiopathology of Aging, University of Bologna	MCI	165(59)	81(51)	76	–	26.3	Diabetes	14
Li L	2012	China	Inpatients in theDepartment of Neurology of Daping Hospital in the city of Chongqing during March–September 2008	MCI	257(96)	111 (43.19)	70.05	–	25.17	Diabetes	34

Solfrizzi V	2004	Italy	the Italian Longitudinal Study on Aging(ILSA)	MCI	121(100)	61 (50.4)	80.7	2.2	21.5	Diabetes	39
Velayudhan L	2010	UK	local primary care practices in south London	MCI	103(59)	66 (64)	79.4	10.6	26.3	Diabetes	42
Xu W	2010	Sweden	A population-based prospective cohort study on aging and dementia, including all registered inhabitants who were age⩾ 75 years and living in the Kungsholmen district of central Stockholm, Sweden	MCI	302(100)	203 (75.7)	82.1	–	24.7	Diabetes	48
Clerici F	2012	Sweden	A memory clinic (the Center for Research and Treatment of Cognitive Dysfunctions of the University of Milan)	MCI	257(95)	143 (58)	74.1	–	25.7	Diabetes	49
Viticchi G	2012	Italy	dementia outpatient service	MCI	117(100)	57(48.7)	75.7	7.4	27.02	Diabetes	50
Ma F	2014	China	6 communities with high proportions of elderly residentswere selected	MCI	690(91)	311(49)	75.27	9.63	–	Diabetes	90

			fromwithin Tianjin city,China								
Ravaglia G	2006	Italy	Center for Physiopathology of Aging, University of Bologna	MCI	165(59)	81(51)	76	–	26.3	Cardiovascular disease	14
Solfrizzi V	2004	Italy	the Italian Longitudinal Study on Aging(ILSA)	MCI	121(100)	61 (50.4)	80.7	2.2	21.5	Cardiovascular disease	39
Velayudhan L	2010	UK	local primary care practices in south London	MCI	103(59)	66 (64)	79.4	10.6	26.3	Cardiovascular disease	42
Clerici F	2012	Sweden	A memory clinic (the Center for Research and Treatment of Cognitive Dysfunctions of the University of Milan)	MCI	257(95)	143 (58)	74.1	–	25.7	Cardiovascular disease	49
Ravaglia G	2006	Italy	Center for Physiopathology of Aging, University of Bologna	MCI	165(59)	81(51)	76	–	26.3	Cerebrovascular disease	14
Solfrizzi V	2004	Italy	the Italian Longitudinal Study on Aging(ILSA)	MCI	121(100)	61 (50.4)	80.7	2.2	21.5	Cerebrovascular disease	39
Velayudhan L	2010	UK	local primary care practices in south London	MCI	103(59)	66 (64)	79.4	10.6	26.3	Cerebrovascular disease	42

Staekenborg SS	2009	Netherlands	outpatient memory clinic of the Alzheimer Centre of the VU University Medical Centre	MCI	152（100）	71（46.7）	69.9	–	26.5	Cerebrovascular disease	44
Clerici F	2012	Sweden	A memory clinic (the Center for Research and Treatment of Cognitive Dysfunctions of the University of Milan)	MCI	257(95)	143 (58)	74.1	–	25.7	Cerebrovascular disease	49
Ravaglia G	2006	Italy	Center for Physiopathology of Aging, University of Bologna	MCI	165(59)	81(51)	76	–	26.3	Atrial fibrillation	14
Forti P	2007	Italy	Center for Physiopathology of Aging, University of Bologna	MCI	180(100)	92(51)	75.7	–	26.2	Atrial fibrillation	17
Clerici F	2012	Sweden	A memory clinic (the Center for Research and Treatment of Cognitive Dysfunctions of the University of Milan)	MCI	257(95)	143 (58)	74.1	–	25.7	Atrial fibrillation	49
Ravaglia G	2006	Italy	Center for Physiopathology of Aging, University of Bologna	MCI	165(59)	81(51)	76	–	26.3	Hypercholesterolemia	14
Sepe-Monti M	2007	Italy	memory clinic of the Department of Neurological Sciences of the University of Rome 'La Sapienza'	aMCI	21(100)	13(62)	72.6	10.1	26.9	Hypercholesterolemia	18

Clerici F	2012	Sweden	A memory clinic (the Center for Research and Treatment of Cognitive Dysfunctions of the University of Milan)	MCI	257(95)	143 (58)	74.1	–	25.7	Hypercholesterolemia	49
Viticchi G	2012	Italy	dementia outpatient service	MCI	117(100)	57(48.7)	75.7	7.4	27.02	Hypercholesterolemia	50
Ravaglia G	2006	Italy	Center for Physiopathology of Aging, University of Bologna	MCI	165(59)	81(51)	76	–	26.3	High body mass index	14
Chu L	2012	Hong Kong	ambulatory setting	aMCI	138(100)	–	–	–	–	High body mass index	24
Clerici F	2012	Sweden	A memory clinic (the Center for Research and Treatment of Cognitive Dysfunctions of the University of Milan)	MCI	257(95)	143 (58)	74.1	–	25.7	High body mass index	49
Barnes DE	2014	USA	Alzheimer's Disease Neuroimaging Initiative 1	aMCI	382(100)	137 (36)	75	–	–	High body mass index	51
van Rossum IA	2012	Netherlands	The VU University Medical Center Alzheimer Center and the Development of Screening Guidelines and Criteria for Predementia Alzheimer's Disease study	MCI	110(99)	51 (46)	70.8	10.8	26.3	Hippocampal atrophy	1

Landau SM	2010	USA	Alzheimer’s Disease Neuroimaging Initiative	MCI	400(21)	29(34.12)	78.1	16.3	27	Hippocampal atrophy	8
Devanand DP	2007	USA	Memory Disorders Center at New York State Psychiatric Institute and Columbia-Presbyterian Medical Center	MCI	139(100)	78(56)	67.1	15.3	27.6	Hippocampal atrophy	19
Jack CR	2010	USA	Alzheimer’s Disease Neuroimaging Initiative	MCI	218(100)	72 (33)	75	16	27	Hippocampal atrophy	20
Prins ND	2013	Netherlands	at a total of 177 centers in 16 countries	MCI	426(100)	233(55)	71	–	–	Medial temporal lobe atrophy	2
Geroldi C	2006	Italy	Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Scientific Institute for Research and Care Brescia, Italy	MCI	52（100）	29（56）	70	7.2	27.2	Medial temporal lobe atrophy	41
van Rossum IA	2012	Netherlands	Memory clinic of the Alzheimer Center of the VU University Medical Center	MCI	248（82）	90（44）	71	11	27	Medial temporal lobe atrophy	43
Staekenborg SS	2009	Netherlands	outpatient memory clinic of the Alzheimer Centre of the VU University Medical Centre	MCI	152（100）	71（46.7）	69.9	–	26.5	Medial temporal lobe atrophy	44

Devanand DP	2007	USA	Memory Disorders Center at New York State Psychiatric Institute and Columbia-Presbyterian Medical Center	MCI	139(100)	78(56)	67.1	15.3	27.6	Entorhinal atrophy	19
Desikan RS	2008	USA	the printmedia	MCI	129(100)	81(62.8)	72.43	15.5	29.1	Entorhinal atrophy	29
Barnes DE	2014	USA	Alzheimer's Disease Neuroimaging Initiative 1	aMCI	382(100)	137 (36)	75	–	–	Entorhinal atrophy	51
Farias STP	2009	USA	Among the participants, 46% were recruited from a clinical setting and 54% were recruited directly through community outreach	MCI	111(100)	57(51)	75.3	12.2	25.9	White matter hyperintensity volume	27
DeCarli C	2004	USA	A prospective longitudinal research project examining the role of CVD and AD on cognition	MCI	52(75)	15(29)	72.8	14.8	–	White matter hyperintensity volume	40
Staekenborg SS	2009	Netherlands	outpatient memory clinic of the Alzheimer Centre of the VU University Medical Centre	MCI	152（100）	71（46.7）	69.9	–	26.5	White matter hyperintensity volume	44

Vemuri P	2011	USA	Mayo Clinic AD Research Center	aMCI	296(42)	51 (41.5)	77	15	27	White matter hyperintensity volume	45
Straaten EC	2008	Netherlands	69 Alzheimer's Disease Cooperative Study (ADCS) centers in the United States and Canada	MCI	152(100)	70(45.8)	72.5	15	27.9	White matter hyperintensity volume	47
Kantarci K	2009	USA	Mayo Clinic Alzheimer's Disease Research Center and Patient Registry	MCI	151(100)	62 (41)	77	14	27	Subcortical infarctions	21
Geroldi C	2006	Italy	Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Scientific Institute for Research and Care Brescia, Italy	MCI	52（100）	29（56）	70	7.2	27.2	Subcortical infarctions	41
Vemuri P	2011	USA	Mayo Clinic AD Research Center	aMCI	296(42)	51 (41.5)	77	15	27	Subcortical infarctions	45
Heister D	2011	USA	Alzheimer's Disease Neuroimaging Initiative (ADNI) database	MCI	192(100)	65(34)	74.6	15.8	26.9	Abnormal CSF Aβ	12
McEvoy L	2011	USA	Alzheimer's Disease Neuroimaging Initiative	MCI	178(100)	–	–	–	–	Abnormal CSF Aβ	23
van Rossum IA	2012	Netherlands	Memory clinic of the Alzheimer Center of the VU	MCI	248（82）	90（44）	71	11	27	Abnormal CSF Aβ	43

			University Medical Center								
van Rossum IA	2012	Netherlands	The VU University Medical Center Alzheimer Center and the Development of Screening Guidelines and Criteria for Predementia Alzheimer's Disease study	MCI	110(99)	51 (46)	70.8	10.8	26.3	Abnormal CSF p-tau	1
Landau SM	2010	USA	Alzheimer's Disease Neuroimaging Initiative	MCI	400(21)	29(34.12)	78.1	16.3	27	Abnormal CSF p-tau	8
Heister D	2011	USA	Alzheimer's Disease Neuroimaging Initiative (ADNI) database	MCI	192(100)	65(34)	74.6	15.8	26.9	Abnormal CSF p-tau	12
van Rossum IA	2012	Netherlands	Memory clinic of the Alzheimer Center of the VU University Medical Center	MCI	248（82）	90（44）	71	11	27	Abnormal CSF p-tau	43
van Rossum IA	2012	Netherlands	The VU University Medical Center Alzheimer Center and the Development of Screening Guidelines and Criteria for Predementia Alzheimer's Disease study	MCI	110(99)	51 (46)	70.8	10.8	26.3	Abnormal CSF t-tau	1
Heister D	2011	USA	Alzheimer's Disease Neuroimaging Initiative (ADNI) database	MCI	192(100)	65(34)	74.6	15.8	26.9	Abnormal CSF t-tau	12
van	2012	Netherla	Memory clinic of the	MCI	248（82）	90（44）	71	11	27	Abnormal CSF t-tau	43

Rossum IA		nds	Alzheimer Center of the VU University Medical Center									
Landau SM	2010	USA	Alzheimer's Disease Neuroimaging Initiative	MCI	400(21)	29(34.12)	78.1	16.3	27	Abnormal CSF tau/A-beta 1–42		8
Heister D	2011	USA	Alzheimer's Disease Neuroimaging Initiative (ADNI) database	MCI	192(100)	65(34)	74.6	15.8	26.9	Abnormal CSF tau/A-beta 1–42		12
McEvoy L	2011	USA	Alzheimer's Disease Neuroimaging Initiative	MCI	178(100)	–	–	–	–	Abnormal CSF tau/A-beta 1–42		23
Gomar JJ	2014	USA	Alzheimer's Disease Neuroimaging Initiative database	MCI	371(100)	174(47)	74.97	15.7	27.07	Abnormal CSF tau/A-beta 1–42		58
Ravaglia G	2006	Italy	Center for Physiopathology of Aging, University of Bologna	MCI	165(59)	81(51)	76	–	26.3	Lower MMSE score		14
van Rossum IA	2012	Netherlands	Memory clinic of the Alzheimer Center of the VU University Medical Center	MCI	248（82）	90（44）	71	11	27	Lower MMSE score		43

Vemuri P	2011	USA	Mayo Clinic AD Research Center	aMCI	296(42)	51 (41.5)	77	15	27	Lower MMSE score	45
Prins ND	2013	Netherlands	at a total of 177 centers in 16 countries	MCI	426(100)	233(55)	71	–	–	Higher score ADAS-Cog	2
Zhou B	2012	Japan	Alzheimer's Disease Neuroimaging Initiative database	MCI	397(100)	141(35.5)	74.8	15.7	–	Higher score ADAS-Cog	28
Rozzini L	2006	Italy	Center of Neurodegenerative and Aging related Disease of the Neurological Clinic, University of Brescia, Italy	aMCI	74	54(73)	71.6	7.6	26.4	Higher score ADAS-Cog	32
Rozzini L	2007	Italy	Center of Neurodegenerative and Aging related Disease of the Neurological Clinic, University of Study, Brescia, Italy	aMCI	119(100)	74(62.2)	70.6	7.8	26.9	Higher score ADAS-Cog	36
Barnes DE	2014	USA	Alzheimer's Disease Neuroimaging Initiative database	aMCI	382	137 (36)	75	–	–	Higher score ADAS-Cog	51

Gomar JJ	2014	USA	Alzheimer's Disease Neuroimaging Initiative database	MCI	371(100)	174(47)	74.97	15.7	27.07	Higher ADAS-Cog score	58	
Landau SM	2010	USA	Alzheimer's Disease Neuroimaging Initiative database	MCI	400(21)	29(34.12)	78.1	16.3	27	Higher AVLT total score	8	
Zhou B	2012	Japan	Alzheimer's Disease Neuroimaging Initiative database	MCI	397(100)	141(35.5)	74.8	15.7	–	Higher AVLT total score	28	
Vemuri P	2011	USA	Mayo Clinic AD Research Center	aMCI	296(42)	51 (41.5)	77	15	27	Higher AVLT total score	45	
Gomar JJ	2014	USA	Alzheimer's Disease Neuroimaging Initiative database	MCI	371(100)	174(47)	74.97	15.7	27.07	Higher AVLT total score	58	
Gomar JJ	2011	USA	Alzheimer's Disease Neuroimaging Initiative database	MCI	320(100)	117(36.6)	74.9	15.6	27.06	Higher AVLT delay score	10	

Zhou B	2012	Japan	Alzheimer’s Neuroimaging database	Disease Initiative	MCI	397(100)	141(35.5)	74.8	15.7	–	Higher AVLT delay score	28			

AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; MCI, mild cognitive impairment; FU, follow-up length; MMSE, mini-mental state examination

Table s-3: Characteristics of cohort studies included in meta-analysis

First author	Year	Country	Exposure	Exposure assessment	Mean follow-up years	Converters to dementia (% AD)	Adjusted for	Relative risk (95% CI)	e-Ref
Petersen RC	1995	USA	Older age	at day of study entry	1.5	25(-)	–	0.99 (0.92, 1.06)	16
Amieva H	2004	France	Older age	at day of study entry	2	29	age and the significant neuropsychological variables	1.09 (0.99, 1.19)	30
Aggarwal NT	2005	USA	Older age	at day of study entry	5.7	82(96)	sex	1.1 (1.06, 1.14)	33
Li L	2012	China	Older age	at day of study entry	3	86(60)	–	1.013 (0.966, 1.063)	34
Alegret M	2014	Spain	Older age	at day of study entry	4	25(100)	–	1.13 (1.02, 1.25)	35
Rozzini L	2007	Italy	Older age	at day of study entry	1	40(100)	–	1.1 (0.9, 1.2)	36
Wang P-N	2014	Taiwan	Older age	at day of study entry	3.54	74（95）	age, sex, education and MMSE scores at baseline	1.1 (1.0, 1.2)	37
Chan WC	2011	Hong Kong	Older age	at day of study entry	2	51(-)	–	1.08 (1.04, 1.13)	38
Solfrizzi V	2004	Italy	Older age	at day of study entry	3.5	–	–	0.59 (0.18, 2.25)	39
DeCarli C	2004	USA	Older age	at day of study entry	3.1	17(59)	age, education, and gender	1.00 (0.92, 1.10)	40
Geroldi C	2006	Italy	Older age	at day of study entry	1.28	11（-）	–	1.0 (0.9, 1.1)	41
Velayudhan L	2010	UK	Older age	at day of study entry	4	19(84)	stroke/TIA, age and gender	1.0 (0.9, 1.1)	42

Li L	2012	Italy	Older age	at day of study entry	1	21(100)	–	1.30 (0.74, 2.28)	50
Inzelberg R	2015	Israel	Older age	at day of study entry	⩾1	68(93)	-	1.18(1.1-1.27)	91
Alegret M	2013	Netherlands	Sex (female)	–	2	81(-)	age and gender forced into the model	1.32 (0.83, 2.1)	2
Rozzini L	2007	Italy	Sex (female)	–	1	40(100)	–	1.4 (0.3, 7.5)	36
Wang P-N	2014	Taiwan	Sex (female)	–	3.54	74（95）	age, sex, education and MMSE scores at baseline	1.8 (0.8, 3.2)	37
Chan WC	2011	Hong Kong	Sex (female)	–	2	51(-)	–	0.89 (0.37, 2.14)	38
Solfrizzi V	2004	Italy	Sex (female)	–	3.5	–	–	0.56 (0.15, 1.88)	39
DeCarli C	2004	USA	Sex (female)	–	3.1	17(59)	age, education, and gender	1.96 (0.59, 6.52)	40
Geroldi C	2006	Italy	Sex (female)	–	1.28	11（-）	–	0.7 (0.2, 2.6)	41
Velayudhan L	2010	UK	Sex (female)	–	4	19(84)	stroke/TIA, age and gender	2.3 (0.8, 7.2)	42
Vemuri P	2011	USA	Sex (female)	–	–	70(81)	age, education, and gender	1.8 (1.0, 3.0)	45

Viticchi G	2012	Italy	Sex (female)	–	1	21(100)	–	0.46 (0.15, 1.44)	50
Barnes DE	2014	USA	Sex (female)	–	–	179（100）	–	1.33 (0.96, 1.84)	51
Ye BS	2012	Republic of Korea	Higher education level	higher education (>8years)	1.43	62(100)	Age, gender, and baseline MMSE scores	2.18 (1.1, 4.32)	26
Rozzini L	2006	Italy	Higher education level	higher education (>5years)	1	39(100)	–	4.2 (1.1, 16.8)	32
Aggarwal NT	2005	USA	Higher education level	–	5.7	82(96)	sex	0.992 (0.924, 1.066)	33
Chan WC	2011	Hong Kong	Higher education level	–	2	51(-)	–	0.98 (0.87, 1.09)	38
DeCarli C	2004	USA	Higher education level	–	3.1	17(59)	age, education, and gender	0.98 (0.78, 1.24)	40
Geroldi C	2006	Italy	Higher education level	–	1.28	11（-）	–	1.1 (0.9, 1.2)	41
Velayudhan L	2010	UK	Higher education level	–	4	19(84)	Unadjusted	1.1 (0.9, 1.1)	42
Viticchi G	2012	Italy	Higher education level	–	1	21(100)	–	0.98656 (0.79457, 1.22493)	50
Xu WL	2012	Sweden	At least 1 APOEε4 allele	microsequencing method	9	118(85)	age, gender, and education.	1.06 (0.76, 1.76)	3

Blacker D	2007	USA	At least 1 APOEε4 allele	Restriction isotyping	5.6	87(79)	age, sex, and education	1.50 (0.91, 2.43)	4
Elcoroaristizabal Martin X	2012	Spain	At least 1 APOEε4 allele	a standard phenol/chloroform extraction method and PCR	3.25	21(100)	age and gender	2.55 (1.20, 5.42)	5
Viticchi G	2014	Italy	At least 1 APOEε4 allele	nucleic acid isolation system and PCR	1	30(–)	gender, basal MMSE, age, education, hypertension diabetes, dyslipidemia, and smoking	6.818 (1.894, 24.545)	6
Squitti R	2014	Italy	At least 1 APOEε4 allele	Restriction isotyping	6	42(100)	–	1.4 (0.7, 2.8)	7
Landau SM	2010	USA	At least 1 APOEε4 allele	–	3	28(100)	Age, education, and sex	1.94 (0.89, 4.21)	8
Devanand DP	2005	USA	At least 1 APOEε4 allele	Restriction isotyping	2.93	35(100)	sex, age, education, baseline MMSE score and SRT delayed recall score	2.0 (0.9, 4.4)	9

Chu LW	2012	Hong Kong	At least 1 APOEε4 allele	–	1	40(100)	–	2.51 (1.01, 6.25)	11
Forlenza OV	2010	Brazil	At least 1 APOEε4 allele	using the TaqMan® 5’-exonuclease allelic discrimination assay obtained from Applied Biosystems with primers and probes sets from inventoried assays	5	13(100)	–	2.3 (1.1, 4.8)	13
Ravaglia G	2006	Italy	At least 1 APOEε4 allele	PCR	3	48(71)	age, gender and education.	4.22 (1.32, 13.5)	14
Diniz BS	2010	Brazil	At least 1 APOEε4 allele	using the TaqMan® 5’-exonuclease allelic discrimination assay obtained from Applied Biosystems with primers and probes sets from inventoried assays	1.58	12(100)	–	4.23 (0.97, 18.42)	15
Petersen RC	1995	USA	At least 1 APOEε4 allele	a DNA extractor (Applied Biosystem 340A DNA Extractor,Applied Biosystems, Foster City, Calif) and PCR	1.5	25(-)	–	4.36 (1.41, 13.54)	16
Aggarwal NT	2005	USA	At least 1 APOEε4 allele	Restriction isotyping	5.7	82(96)	age, gender, and education	1.948 (1.196, 3.173)	33

Alegret M	2014	Spain	At least 1 APOEε4 allele	PCR	4	25(100)	age and education	4.22 (0.89, 19.84)	35
Wang P-N	2014	Taiwan	At least 1 APOEε4 allele	PCR amplification and restriction isotyping	3.54	74（95）	age, sex, education and MMSE scores at baseline	2 (1.2, 3.3)	37
Vemuri P	2011	USA	At least 1 APOEε4 allele	–	–	70(81)	age, sex, and education	1.8 (1.0, 3.1)	45
Barnes DE	2014	USA	At least 1 APOEε4 allele	–	–	179（100）	–	1.86 (1.36, 2.56)	51
Steenland K	2012	USA	At least 1 APOEε4 allele	–	2.5	950（100）	age, gender, race, education, history of hypertension, of diabetes, and of heart disease	1.68 (1.44, 1.96)	55
Xu WL	2012	Sweden	APOEε4ε4	microsequencing method	9	118(85)	age, gender, and education.	2.53 (1.01,6.48)	3
Blacker D	2007	USA	APOEε4ε4	Restriction isotyping	5.6	87(79)	age, sex, and education	1.64 (1.05, 2.57)	4

Elcoroaristizabal Martin X	2012	Spain	APOEε4ε4	a standard phenol/chloroform extraction method and PCR	3.25	21(100)	age and gender	10.34 (2.94, 36.43)	5
Ravaglia G	2006	Italy	Smoking	Smoking habit was dichotomized as never smokers versus ex-smokers and current smokers	3	48(71)	age, gender and education.	0.54 (0.22, 1.32)	14
Sepe-Monti M	2007	Italy	Smoking	Smoking:more than five cigarettes per day for at least 5 years;Not smoking: less than five cigarettes per day or stopped smoking for 10 years.	2.5	10(100)	–	0.4 (0.1, 2.2)	18
Fellows L	2008	Canada	Smoking	A standardized clinical history	5.9	50(100)	–	0.98 (0.95, 1.00)	31
Solfrizzi V	2004	Italy	Smoking	screening questionnaire	3.5	–	–	0.46 (0.08, 1.74)	39
Velayudhan L	2010	UK	Smoking	self-report	4	19(84)	Unadjusted	0.8 (0.17, 4.3)	42

Clerici F	2012	Sweden	Smoking	Smoking habit was dichotomized as never smokers versus ex-smokers and current smokers	2.3	129(68)	age, gender and education.	1.4 (0.9, 2.3)	49
Viticchi G	2012	Italy	Smoking	smoking was defined as a history of active tobacco smoking	1	21(100)	–	0.41 (0.09, 1.90)	50
Somme J	2013	Spain	Anxiety	NPI	3.5	43(-)	–	2.9 (1.2, 6.9)	22
Palmer K	2007	Sweden	Anxiety	CPRS	3	27(89)	baseline cognitive status	1.9 (1.2, 2.8)	25
Ramakers IHGB	2010	Netherlands	Anxiety	HAMD	5.4	90(88)	age, sex and education	0.58 (0.34, 1.0)	56
Somme J	2013	Spain	Apathy	NPI	3.5	43(-)	–	2.4 (1.9, 4.9)	22
Chan WC	2011	Hong Kong	Apathy	NPI	2	51(-)	–	0.31 (0.09, 1.13)	38
Richard E	2012	Netherlands	Apathy	3 apathy items of the 15-item Geriatric Depression Scale	2.7	166(100)	age, gender, education and baseline MMSE score	1.85 (1.09, 3.15)	46
Ramakers IHGB	2010	Netherlands	Apathy	HAMD	5.4	90(88)	age, sex and education	0.67 (0.40, 1.13)	56
Golimstok A	2013	Argentina	Apathy	NPI	6.3	–	–	6.5 (2, 20)	57

Chan WC	2011	Hong Kong	Depression	NPI	2	51(-)	–	2.40 (1.05, 5.46)	38
Geroldi C	2006	Italy	Depression	Center for Epidemiological Studies Depression (CES-D) scale	1.28	11（-）	–	1.1 (0.9, 1.1)	41
Velayudhan L	2010	UK	Depression	Geriatric Depression Scale (GDS)	4	19(84)	Unadjusted	1.4 (0.5, 3.9)	42
Richard E	2012	Netherlands	Depression	Geriatric Depression Scale (GDS)	2.7	166(100)	age, gender, education and baseline MMSE score	1.15 (0.72, 1.83)	46
Panza F	2008	Italy	Depression	Geriatric Depression Scale (GDS)	3.5	14(-)	–	1.42 (0.48, 4.23)	52
Modrego PJ	2004	Spain	Depression	Geriatric Depression Scale (GDS)	5.2	59(-)	–	2.6 (1.8,3.6)	53
Richard EM	2008	Italy	Depression	Center for Epidemiological Studies Depression (CES-D) scale	5.1	67(-)	age and sex	1.9 (1.0, 3.6)	54

Steenland K	2012	USA	Depression	–	2.5	950（100）	age, gender, race, education, history of stroke/TIA, history of diabetes, four cognitive tests(MMSE, logical memory, category fluency, WAIS), and FAQ	1.21 (1.00, 1.46)	55
Ramakers IHGB	2010	Netherlands	Depression	HAMD	5.4	90(88)	age, sex and education	0.61 (0.36, 1.01)	56
Ravaglia G	2006	Italy	Hypertension	Hypertension was defined as a systolic blood pressure ⩾ 140 mm Hg, a diastolic blood pressure⩾90 mm Hg	3	48(71)	age, gender and education.	1.25 (0.70, 2.45)	14
Sepe-Monti M	2007	Italy	Hypertension	history of blood pressure measurements greater than 160/95 mmHg or antihypertensive medication intake	2.5	10(100)	–	2.6 (0.4, 15.3)	18

Li L	2012	China	Hypertension	Hypertension was defined as systolic blood pressure ⩾ 140 mm Hg and/or diastolic blood pressure⩾90 mm Hg	3	86(60)	–	0.74 (0.15, 3.73)	34
Solfrizzi V	2004	Italy	Hypertension	either a self-reported diagnosis or medical treatment or a recorded mean diastolic value⩾ 90 mm Hg or a systolic value⩾ 140 mm Hg	3.5	–	–	1.74 (0.46, 9.74)	39
Clerici F	2012	Sweden	Hypertension	hypertension was defined as systolic blood pressure ⩾140 mm Hg and/or diastolic blood pressure ⩾90 mm Hg and/or use of antihypertensive medication	2.3	129(68)	age, gender and education.	1.3 (0.8, 1.9)	49
Viticchi G	2012	Italy	Hypertension	a history of high blood pressure, a systolic blood pressure⩾140 mm Hg, a diastolic blood pressure⩾90 mm Hg, or the use of an antihypertensive	1	21(100)	–	0.40 (0.11, 1.51)	50
Inzelberg R	2015	Israel	Hypertension	a systolic blood pressure⩾140 mm Hg, a diastolic blood pressure⩾90 mm Hg	⩾1	68(93)	-	1.18(1.1-1.27)	91

Ravaglia G	2006	Italy	Diabetes	medical history as provided by the patients and conirmed by clinical evaluation	3	48(71)	age, gender and education.	0.75 (0.26, 2.13)	14
Li L	2012	China	Diabetes	Diabetes was a concentration of fasting plasma glucose ⩾ 7.0 mmol/l (126 mg/dl)	3	86(60)	–	2.92 (1.12, 7.60)	34
Solfrizzi V	2004	Italy	Diabetes	self-reported diagnosis (diagnosis by a physician or medical treatment), or of a fasting plasma glucose level⩾ 7.8 mmol/L, on at least two separate days	3.5	–	–	0.54 (0.01, 3.62)	39
Velayudhan L	2010	UK	Diabetes	a report of physician diagnosis of the disorder with evidence of use of oral antidiabetic medications or insulin and information from the general practitioner	4	19(84)	stroke/TIA,age and gender	2.9 (1.1, 7.3)	42

Xu W	2010	Sweden	Diabetes	Diabetes was identified by clinical examination and through the inpatient register system, use of hypoglycemic drugs, and random blood glucose level⩾11.0 mmol/l	9	137(-)	age, sex, education, baseline MMSE score, BMI, heart disease, stroke, systolic blood pressure, diastolic blood pressure, follow-up survival status, and APOE genotype	2.83 (1.18, 6.78)	48
Clerici F	2012	Sweden	Diabetes	diabetes mellitus was defined as having a fasting venous plasma glucose level ⩾ 126 mg/dl and/or treatment for diabetes mellitus	2.3	129(68)	age, gender and education.	1.3 (0.8, 2.0)	49
Viticchi G	2012	Italy	Diabetes	diabetes mellitus was defined as a history of diabetes mellitus, a fasting serum glucose>7.0 mmol/L(1.26 g/L), or the use of an oral antihyperglycemic or insulin	1	21(100)	–	1.30 (0.36, 4.66)	50

Ma F	2014	China	Diabetes	treatment for diabetes reported in a questionnaire; a physician’s diagnosis of diabetes-related complications;or a fasting blood glucose ⩾ 126mg/dL (⩾ 7.0mmol/L) reported 2 or more times.	5	152(43)	age and gender	1.417(1.346-1.493)	90
Ravaglia G	2006	Italy	Cardiovascular disease	history of myocardial infarction, angina, peripheral vascular disease and congestive heart failure	3	48(71)	age, gender and education.	0.90 (0.44, 1.84)	14
Solfrizzi V	2004	Italy	Cardiovascular disease	coronary arteriography showing>70% obstruction of any coronary artery, or ST depression>1 mm on exercise testing	3.5	–	–	1.71 (0.32, 6.78)	39
Velayudhan L	2010	UK	Cardiovascular disease	myocardial infarction, angina and coronary artery bypass grafting	4	19(84)	Unadjusted	1.1 (0.4, 2.8)	42
Clerici F	2012	Sweden	Cardiovascular disease	history of angina, myocardial infarction, heart failure, or claudicatio intermittens	2.3	129(68)	age, gender and education.	0.6 (0.3,1.1)	49
Ravaglia G	2006	Italy	Cerebrovascular disease	history of stroke or TIA	3	48(71)	age, gender and education.	2.01 (0.69, 5.88)	14

Solfrizzi V	2004	Italy	Cerebrovascular disease	WHO criteria	3.5	–	–	4.00 (0.92, 13.87)	39
Velayudhan L	2010	UK	Cerebrovascular disease	–	4	19(84)	age and gender	2.8 (0.9, 9.3)	42
Staekenborg SS	2009	Netherlands	Cerebrovascular disease	different MRI sequences	1.99	72（78）	age and gender	1.1 (0.3, 3.8)	44
Clerici F	2012	Sweden	Cerebrovascular disease	history of stroke or transient ischemic attack	2.3	129(68)	age, gender and education.	1.0 (0.6, 1.7)	49
Ravaglia G	2006	Italy	Atrial fibrillation	medical history as provided by the patients and confirmed by clinical evaluation	3	48(71)	age, gender and education.	8.06 (3.43, 18.94)	14
Forti P	2007	Italy	Atrial fibrillation	medical history as provided by the patients and confirmed by clinical evaluation	2.8	52(71)	age, gender, education, baseline MMSE score, MCI subtype, diastolic blood pressure, BMI and serum folate	4.63 (1.72, 12.46)	17
Clerici F	2012	Sweden	Atrial fibrillation	medical history, as provided by the patients and confirmed by clinical evaluation	2.3	129(68)	age, gender and education.	0.5 (0.3, 1.2)	49

Ravaglia G	2006	Italy	Hypercholesterolemia	Serum total cholesterol was measured on fresh venous blood samples total cholesterol ⩾ 6.6 mmol/L	3	48(71)	age, gender and education.	0.29 (0.09, 0.87)	14
Sepe-Monti M	2007	Italy	Hypercholesterolemia	serum cholesterol level over 220 mg/dl or statin intake	2.5	10(100)	–	0.1 (0.1, 0.5)	18
Clerici F	2012	Sweden	Hypercholesterolemia	a fasting plasma total cholesterol level ⩾ 190 mg/dl and/or treatment for hypercholesterolemia	2.3	129(68)	age, gender and education.	1.2 (0.8, 1.9)	49
Viticchi G	2012	Italy	Hypercholesterolemia	fasting serum total cholesterol ⩾ 6.22 mmol/L (2.4 g/L) or triglycerides ⩾ 2.26 mmol/L (2 g/L), or the use of a statin or fibrate	1	21(100)	–	1.50 (0.50, 4.44)	50
Ravaglia G	2006	Italy	High body mass index	calculated as weight in kilograms divided by the square of the height in meters, cutoff: ⩾ 30.0	3	48(71)	age, gender and education.	0.62 (0.26, 1.46)	14
Chu L	2012	Hong Kong	High body mass index	calculated as weight in kilograms divided by the square of the height in meters	3	35(100)	age, sex and apolipoprotein E genotype	0.88 (0.77, 0.99)	24

Clerici F	2012	Sweden	High body mass index	calculated as weight in kilograms divided by the square of the height in meters, cutoff:⩾ 30.0	2.3	129(68)	age, gender and education.	0.9 (0.5,1.8)	49
Barnes DE	2014	USA	High body mass index	calculated as weight in kilograms divided by the square of the height in meters, cutoff:⩾ 22	–	179（100）	–	0.68 (0.47, 0.99)	51
van Rossum IA	2012	Netherlands	Hippocampal atrophy	Learning embeddings for atlas propagation(LEAP), cut off point for 5.39 cm3	2.2	109(58)	Age, gender, and education	2.2 (1.0, 5.0)	1
Landau SM	2010	USA	Hippocampal atrophy	Tructural magnetic resonance scans(1.5-T) and Freesurfer software	3	28(100)	Age, education, and sex	2.49 (1.02, 5.96)	8
Devanand DP	2007	USA	Hippocampal atrophy	GE 1.5-T Signa 5X unit	5	37	ICV(intracranial volume), sex, education, MMSE	2.89 (1.52, 5.51)	19
Jack CR	2010	USA	Hippocampal atrophy	scanned at 1.5 T with a 3D magnetization preparing rapid acquisition gradient echo imaging sequence	1.7	89(-)	total intracranial volumes	2.6 (1.8, 3.8)	20

Prins ND	2013	Netherlands	Medial temporal lobe atrophy	1.5 T scanners and included a 3-D T1-weighted gradient-echo sequence and a 2-D fast fluid attenuated inversion recovery sequence	2	81(-)	age and gender 可选择	1.87 (1.43, 2.44)	2
Geroldi C	2006	Italy	Medial temporal lobe atrophy	1.0 Tesla Philips Gyroscan(PG) in Brescia, 1.0 Tesla Siemens Impact (SI) in Verona,and 1.5 Tesla Siemens Vision (SV) in Milan and the gradient echo 3D technique	1.28	11（-）	–	8.3 (1.8, 37.3)	41
van Rossum IA	2012	Netherlands	Medial temporal lobe atrophy	1.0 Tesla scanner and included a coronal T1-weighted 3D inversion-prepared gradient echo sequence	2.42	91（100）	Age, gender, and educational level	2.2 (1.3, 3.7)	43
Staekenborg SS	2009	Netherlands	Medial temporal lobe atrophy	1.0-T machine according to a standard protocol, including coronal T1-weighted 3D magnetization prepared rapid acquisition gradient echo	1.99	72（78）	age and sex	2.9 (1.7, 5.3)	44
Devanand DP	2007	USA	Entorhinal atrophy	GE 1.5-T Signa 5X unit	5	37	ICV(intracranial volume), sex, education, MMSE	2.79 (1.75,4.47)	19

Desikan RS	2008	USA	Entorhinal atrophy	1.5T Signa scanner (GE Healthcare, Milwaukee, Wis)	5	44(100)	–	1.59 (1.10, 2.27)	29
Barnes DE	2014	USA	Entorhinal atrophy	–	–	179（100）	–	2.31 (1.30, 4.10)	51
Farias STP	2009	USA	White matter hyperintensity volume	a 1.5-TGE SignaHorizon LX Echospeed system or a 1.5-T Marconi system	2.4	28(-)	–	1.23 (1.02, 1.48)	27
DeCarli C	2004	USA	White matter hyperintensity volume	–	3.1	17(59)	age, education, and gender	0.73 (0.35, 1.54)	40
Staekenborg SS	2009	Netherlands	White matter hyperintensity volume	1.0-T machine according to a standard protocol, including coronal T1-weighted 3D magnetization prepared rapid acquisition gradient echo	1.99	72（78）	age and sex	1.2 (0.7, 2.2)	44
Vemuri P	2011	USA	White matter hyperintensity volume	15 different 1.5 Tesla GESIGNA MRI scanners using a standard transmit–receive volume head coil	–	70(81)	age, education, and gender	1.0 (0.8, 1.2)	45
Straaten EC	2008	Netherlands	White matter hyperintensity volume	A 3D T1-weighted gradient echo sequence and 2D proton density and T2-weighted spin-echo sequences with 24 transverse slices, slice thickness 5 mm	3	55	Age and education	1.03 (0.99, 1.06)	47

Kantarci K	2009	USA	Subcortical infarctions	discrete subcortical lesions>3mm in diameter with intensity that is equivalent to CSF on FLAIR images and accompanying hyperintense gliotic rim	2.1	75(-)	Age, sex and education	0.82 (0.4, 1.9)	21
Geroldi C	2006	Italy	Subcortical infarctions	MRI with the Age-Related White Matter Changes Scale total score >6, or when the beginning of confluence of lesions (score 2) was observed in at least one region	1.28	11（-）	–	2.9 (0.7, 11.4)	41
Vemuri P	2011	USA	Subcortical infarctions	15 different 1.5 Tesla GESIGNA MRI scanners using a standard transmit–receive volume head coil	–	70(81)	age, education, and gender	0.47 (0.1, 1.5)	45
Heister D	2011	USA	Abnormal CSF Aβ	using the multiplex xMAP Luminex platform with Innogenetics immunoassay kitbased reagents,cutoff points for CSF Aβ (192 pg/mL)	2.42	84(100)	Age	3.4 (1.7–6.9	12
McEvoy L	2011	USA	Abnormal CSF Aβ	cutoff: CSF Aβ (192 pg/mL)	3	142(-)	–	3.68 (1.89 ,7.92)	23

van Rossum IA	2012	Netherlands	Abnormal CSF Aβ	InnoTest sandwich ELISA, cutoff points for CSF Aβ (435 pg/ml)	2.42	91（100）	Age, gender, and educational level	0.9 (0.5,1.7)	43
van Rossum IAMD	2012	Netherlands	Abnormal CSF p-tau	InnoTest sandwich ELISA, cutoff points for CSF t-tau (375 pg/mL) and p-tau (52 pg/mL).	2.2	109(58)	Age, gender, and education	3.5 (1.3, 9.2)	1
Landau SM	2010	USA	Abnormal CSF p-tau	–	3	28(100)	Age, education, and sex	2.88 (1.09, 7.59)	8
Heister D	2011	USA	Abnormal CSF p-tau	using the multiplex xMAP Luminex platform with Innogenetics immunoassay kitbased reagents,cutoff points for CSF t-tau (93 pg/mL) and p-tau (23 pg/mL)	2.42	84(100)	Age	2.9 (1.6, 5.3)	12
van Rossum IA	2012	Netherlands	Abnormal CSF p-tau	InnoTest sandwich ELISA, cutoff points for CSF t-tau (627 pg/mL) and p-tau (88 pg/mL).	2.42	91（100）	Age, gender, and educational level	1.7 (0.9, 2.9)	43
van Rossum IAMD	2012	Netherlands	Abnormal CSF t-tau	InnoTest sandwich ELISA, cutoff points for CSF t-tau (375 pg/mL) and p-tau (52 pg/mL).	2.2	109(58)	Age, gender, and education	2.3 (1.1, 4.6)	1

Heister D	2011	USA	Abnormal CSF t-tau	using the multiplex xMAP Luminex platform with Innogenetics immunoassay kitbased reagents,cutoff points for CSF t-tau (93 pg/mL) and p-tau (23 pg/mL)	2.42	84(100)	Age	1.8 (1.1, 2.7)	12
van Rossum IA	2012	Netherlands	Abnormal CSF t-tau	InnoTest sandwich ELISA, cutoff points for CSF t-tau (627 pg/mL) and p-tau (88 pg/mL).	2.42	91（100）	Age, gender, and educational level	1.7 (1.0, 3.2)	43
Landau SM	2010	USA	Abnormal CSF tau/A-beta 1–42	–	3	28(100)	Age, education, and sex	3.99 (1.19, 13.32)	8
Heister D	2011	USA	Abnormal CSF tau/A-beta 1–42	using the multiplex xMAP Luminex platform with Innogenetics immunoassay kitbased reagents	2.42	84(100)	Age	3.8 (1.8, 8.2)	12
McEvoy L	2011	USA	Abnormal CSF tau/A-beta 1–42	cutoff:tau/Aß1-42 ratio=0.39	3	142(-)	–	3.68 (1.89, 7.92)	23
Gomar JJ	2014	USA	Abnormal CSF tau/A-beta 1–42	–	4	150(100)	age, sex and education	2.34 (1.45-3.91)	58
Ravaglia G	2006	Italy	Lower MMSE score	MMSE≤26	3	48(71)	age, gender and education.	2.68 (1.50, 4,79)	14

van Rossum IA	2012	Netherlands	Lower MMSE score	–	2.42	91（100）	Age, gender, and educational level	2.0 (1.2, 3.2)	43
Vemuri P	2011	USA	Lower MMSE score	–	–	70(81)	age, education, and gender	1.2 (1.1, 1.3)	45
Prins ND	2013	Netherlands	Higher ADAS-Cog score	–	2	81(-)	age and gender forced into the model	1.08 (1.06, 1.11)	2
Zhou B	2012	Japan	Higher ADAS-Cog score	–	4.4	164(100)	–	1.12 (1.09, 1.15)	28
Rozzini L	2006	Italy	Higher ADAS-Cog score	ADAS Cog (>13 pts)	1	39(100)	–	9.6 (1.5, 61.6)	32
Rozzini L	2007	Italy	Higher ADAS-Cog score	–	1	40(100)	–	1.4 (1.1, 1.8)	36
Barnes DE	2014	USA	Higher ADAS-Cog score	–	–	179（100）	–	2.9 (1.59, 5.27)	51
Gomar JJ	2014	USA	Higher ADAS-Cog score	–	4	150(100)	age, sex and education	1.08 (1.01-1.15)	58

Landau SM	2010	USA	AVLT score	total	–	3	28(100)	Age, education, and sex	4.30 (1.24, 14,97)	8
Zhou B	2012	Japan	AVLT score	total	–	4.4	164(100)	–	0.76 (0.66, 0.86)	28
Vemuri P	2011	USA	AVLT score	total	–	–	70(81)	age, education, and gender	1.4 (1.2, 1.6)	45
Gomar JJ	2014	USA	AVLT score	total	–	4	150(100)	age, sex and education	0.83 (0.73-0.95)	58
Gomar JJ	2011	USA	AVLT score	delay	–	2	116(100)	–	0.77 (0.64, 0.92)	10
Zhou B	2012	Japan	AVLT score	delay	–	4.4	164(100)	–	0.90 (0.83, 0.99)	28

AD, Alzheimer's disease