

RESEARCH PAPER

Meta-analysis of modifiable risk factors for Alzheimer's disease

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ABSTRACT

Background The aetiology of Alzheimer's disease (AD) is believed to involve environmental exposure and genetic susceptibility. The aim of our present systematic review and meta-analysis was to roundly evaluate the association between AD and its modifiable risk factors.

Methods We systematically searched PubMed and the Cochrane Database of Systematic Reviews from inception to July 2014, and the references of retrieved relevant articles. We included prospective cohort studies and retrospective case-control studies.

Results 16 906 articles were identified of which 323 with 93 factors met the inclusion criteria for meta-analysis. Among factors with relatively strong evidence (pooled population >5000) in our meta-analysis, we found grade I evidence for 4 medical exposures (oestrogen, statin, antihypertensive medications and non-steroidal anti-inflammatory drugs therapy) as well as 4 dietary exposures (folate, vitamin E/C and coffee) as protective factors of AD. We found grade I evidence showing that one biochemical exposure (hyperhomocysteine) and one psychological condition (depression) significantly increase risk of developing AD. We also found grade I evidence indicative of complex roles of pre-existing disease (frailty, carotid atherosclerosis, hypertension, low diastolic blood pressure, type 2 diabetes mellitus (Asian population) increasing risk whereas history of arthritis, heart disease, metabolic syndrome and cancer decreasing risk) and lifestyle (low education, high body mass index (BMI) in mid-life and low BMI increasing the risk whereas cognitive activity, current smoking (Western population), light-to-moderate drinking, stress, high BMI in late-life decreasing the risk) in influencing AD risk. We identified no evidence suggestive of significant association with occupational exposures.

Conclusions Effective interventions in diet, medications, biochemical exposures, psychological condition, pre-existing disease and lifestyle may decrease new incidence of AD.

INTRODUCTION

With complex aetiological profiles underpinned by both major genetic culprits and indispensable environmental contributors, Alzheimer's disease (AD) is the most common type of dementia and neurodegenerative disease. AD leads to an enormous burden on persons and societies.¹ Given that its worldwide prevalence is increasing and that there is currently no cure for the disease, figuring out its modifiable risk factors and investigating how to efficaciously prevent it have always been a pretty hot spot in the field.² On the basis of population attributable risks (PAR), Barnes and Yaffe³

estimated that nearly half of the AD cases globally might be attributable to seven common potentially modifiable risk factors and a marginal (10–25%) reduction of these risk factors could potentially prevent up to 1.1–3.0 million cases worldwide. Recently, two European studies showed that improved physical and cognitive functioning may contribute to a decline in dementia prevalence in the long term. These findings are suggestive of critical roles of adjusting modifiable risk factors in preventing AD incidence.^{4 5} Large amounts of literatures with inconsistent conclusions have been published to investigate potentially modifiable risk factors of AD, confusing our knowledge about this field. Therefore, we have carried out the most extensive and comprehensive systematic review and meta-analysis to date, which employs a full-scale search of observational studies to calculate effect sizes of various modifiable risk factors for AD.

METHODS

Search strategy

We adhere to the recommendations made by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group, the PRISMA 2009 guidelines for systematic review and meta-analysis^{6 7} as well as the Cochrane Collaboration definition of both terms.⁸ We searched PubMed and the Cochrane Database of Systematic Reviews for studies that reported risk factors of AD from August 1968 to July 2014. Search terms were "Alzheimer's disease", "dementia" and "risk factor". We confined our search to papers published in English. Bibliographies of retrieved studies and all relevant reviews, systematic reviews and meta-analyses were hand-searched for further supplement. The final search was carried out on 15 July 2014.

Inclusion criteria

Literatures were included if they simultaneously fulfilled the following criteria: (1) the study reported original data concerning odds ratio (OR) or relative risk (RR) of AD using a longitudinal cohort study or retrospective case-control study design, (2) the study population is representative of the general population and (3) the exposures considered to be positively or negatively associated with later diagnosis of AD are potentially modifiable.

Exclusion criteria

The detailed exclusion criteria have been shown in [figure 1](#). If there was disagreement between

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authors, the articles were discussed in further detail until an agreement was reached.

Data extraction

The general study characteristics and risk estimates of study findings (OR/RR values) relative to AD risk factors were extracted for all eligible studies utilising a standardised template. Only factors for which a significant association was reported in at least one study were included. As different studies might use different exposure categories, data that reported exposures as multiple levels where the lowest level was equal to zero were qualitatively converted to dichotomy (such as highest vs zero/lowest exposure, ever vs never exposure, yes vs no exposure). We did not include studies reporting associations of AD with age, race, gender, family history of genetic disease (such as familiar dementia, AD, Parkinson disease or Down syndrome) and anthropometric index (such as body height, knee height and arm span) as we do not think that these exposures belong to modifiable factors. For controls, we give priority to the randomly selected, larger healthy population without cognitive impairment at baseline if there was more than one control group. For cases, we take precedence to choose patients with AD without cerebrovascular disease. For the analysis model in studies, we give more priorities to multivariate analysis or adjusted OR/RR than univariate analysis or crude results. If exposures were classified in categorical and continuous manners, the former was used. If there was gender stratification, we would treat the results as two independent results with male and female populations separately. If the studies failed to report OR/RR, the raw data were reviewed to determine whether OR/RR could be calculated. After application of the above methods, no additional studies required exclusion for quality reasons, according to the Newcastle-Ottawa scale.

Statistical analysis

Where an exposure of interest was reported by at least two studies in a consistent way, these were combined in a meta-analysis: first separately for case-control and cohort studies (as the latter are less subject to bias), and second for all studies together (regarding OR as estimates of RR) to generate a pooled effect size and 95% CI for each other. Heterogeneity between studies was assessed using the I^2 statistic and where statistically significant heterogeneity was found ($p < 0.05$), it was analysed further. When heterogeneity cannot be explained, the random effect model, which takes variation both within and between studies into consideration, was employed to combine results.^{9–10} Publication bias was evaluated using the Egger test, and where statistically significant bias was found, the trim and fill method was used to adjust it.¹¹ Where data were not given in a way suitable for meta-analysis or where only one significant study was identified for a given risk factor, the results of these findings are as listed in online supplementary table e-3. We used Stata V.12.0 to perform all these analyses.

For potential heterogeneity, we conducted multiple sensitivity analyses to examine if the pooled effect estimate was influenced by removal of any single study or was influenced by characteristics of the study design or population. On the basis of characteristics of studies (such as type of study design, exposure dose, region of population, criteria for AD), we either performed subgroup analyses or removed studies presenting a risk of bias (so-called outlier) and compared the pooled estimates with and without the excluded studies. Where heterogeneity still existed ($p > 0.05$) and could not be further explained, we accepted it and adopted a random effect model to calculate the

overall effect. (The results can be seen in online supplementary table e-4.)

From the perspective of prevention, we calculated PAR, which in our case refers to the proportion of AD cases in a population that can be 'attributed' to a given risk factor. We also calculated a combined PAR, or the pooled effect of simultaneous reduction of all nine risk factors, for which the global prevalence has been reported. The methods of calculation used in our article had been reported by Barnes and Yaffe.³ In addition, we assigned three grades of evidence in support of the conclusion according to two elements including the pooled sample size and heterogeneity: 'grade I evidence' was defined as both pooled population > 5000 and lower heterogeneity ($I^2 < 50\%$); 'grade II-A evidence' was defined as pooled population > 5000 but with higher heterogeneity ($I^2 \geq 50\%$); 'grade II-B evidence' was defined as lower heterogeneity ($I^2 \geq 50\%$) but with pooled population < 5000 ; 'grade III evidence' was defined as both pooled population < 5000 and higher heterogeneity.

RESULTS

Association results from primary analysis

The literature search yielded 15 388 English papers. After reviewing the titles and abstracts, 2009 studies were identified as potentially eligible for inclusion. After reviewing the full article text, 351 (see online supplementary E-references) were eligible for inclusion in the systematic review and 323 (see online supplementary reference list E1-E323) of these in the meta-analysis. Full details of literatures included in the meta-analysis are provided (see online supplementary tables e-1 and e-2).

Summary results for positive and negative associations with AD identified in the primary meta-analysis (see online supplementary tables e-5 and e-6) and those where no association was found (see online supplementary table e-7) are shown. In consideration of the smaller pooled population (< 5000) reported for some factors, here we only presented those for which the pooled population is relatively large (> 5000) to lower the error of estimates. Significant positive and negative associations were found for 13 factors (11 with grade I evidence and 2 with grade II-A evidence) (figure 2A) and 23 factors (18 with grade I evidence and 5 with grade II-A evidence) (figure 2B), respectively. No significant association was found for 23 factors (19 with grade I evidence and 4 with grade II-A evidence) (figure 3). More specifically, we found grade I evidence for four medical exposures (oestrogen, statin, antihypertensive medications and non-steroidal anti-inflammatory drugs (NSAIDs) therapy) as well as four dietary exposures (folate, vitamin E/C and coffee) as protective factors of AD. We found grade I evidence showing that one biochemical exposure (hyperhomocysteine) and one psychological condition (depression) significantly increased the risk of developing AD. We also found grade I evidence indicative of complex roles of pre-existing disease (frailty, carotid atherosclerosis, hypertension, low diastolic blood pressure (DBP), type 2 diabetes mellitus (DM-2; Asian population) increasing risk whereas history of arthritis, heart disease, metabolic syndrome (MS) and cancer decreasing risk) and lifestyle (low education, high body mass index (BMI) in mid-life and low BMI increasing the risk whereas cognitive activity, current smoking (Western population), light-to-moderate drinking, stress, high BMI in late-life decreasing the risk) in influencing AD risk. However, we identified no evidence suggestive of significant association with occupational exposures. The whole selection procedure of factors associated with AD risk with different evidence grade was present in figure 4. More than 61 factors that could not be included in the meta-analysis, primarily due to

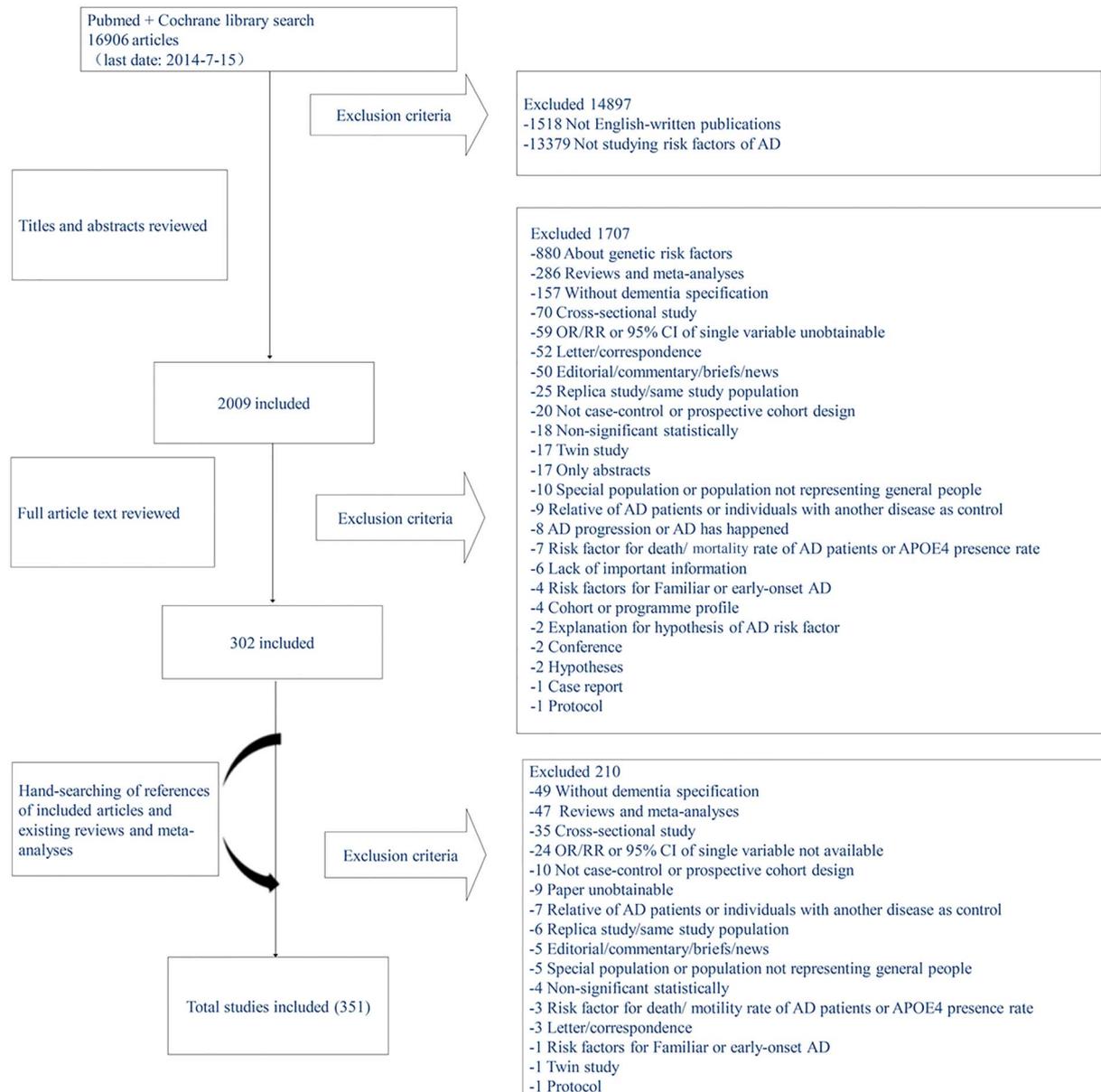


Figure 1 Flow chart of studies included and excluded. We excluded review, systematic review and meta-analysis articles, editorials, commentaries, briefs, news, conferences, cohort or programme profiles, protocols, letters or correspondences that reported no new data. We did not include papers which are not accessible but abstracts. We excluded studies that (1) employed the same population or a replica study. (When >1 literatures employed the same population, we chose the study with larger sample size; when the sample sizes were equal, we chose the study with longer follow-up; when both of these are equal, we chose the study more recently published.), (2) were twin studies, (3) employed relatives of patients with AD or individuals with another specific disease as the control group, (4) only reported data on dementia without specification for AD, (5) made explanations for hypothesis of AD risk factors (6) exclusively reported risk factors for mortality or progression, or the hospitalisation rate of AD, (7) were case-reports, (8) employed special populations not representative of general people (such as patients with some major disease), (9) were cross-sectional studies, (10) studied familiar or early-onset AD only, (11) reported genetic risk factors (such as specific single nucleotide polymorphism, family history of dementia), (12) reported merely OR/RR but not sufficient information about the study procedure (considered as low quality according to the Newcastle-Ottawa scale), (13) reported no measures about OR/RR or some measures other than OR/RR or an equivalent (such as *p* values) (AD, Alzheimer's disease; APOE4, apolipoprotein E4; RR, relative risk).

inconsistency in the method of measuring studied risk factors or because of the scarcity of literatures ($N=1$) reporting that risk factor, are described in online supplementary table e-3.

Heterogeneity and sensitivity analysis

We found 29 factors for which analysis heterogeneity is evident ($p>0.05$) and can be further analysed ($N\geq 3$). Through heterogeneity and sensitivity analyses (see online supplementary table e-4), the statistical significances of the factors which initially

showed positive or negative associations but with a high heterogeneity were not changed (see online supplementary tables e-5A and e-6A).

Specifically, for high BMI in mid-life, the heterogeneity was reduced to 11.5% and the pooled effect was mildly lowered (RR from 1.65 to 1.20) when one single study which did not report specific criteria for AD was excluded. Also, the subgroup analysis ($BMI\geq 30$) showed an increased risk for AD (RR from 1.5 to 1.72) with an acceptable heterogeneity ($I^2=42.0\%$), suggesting a

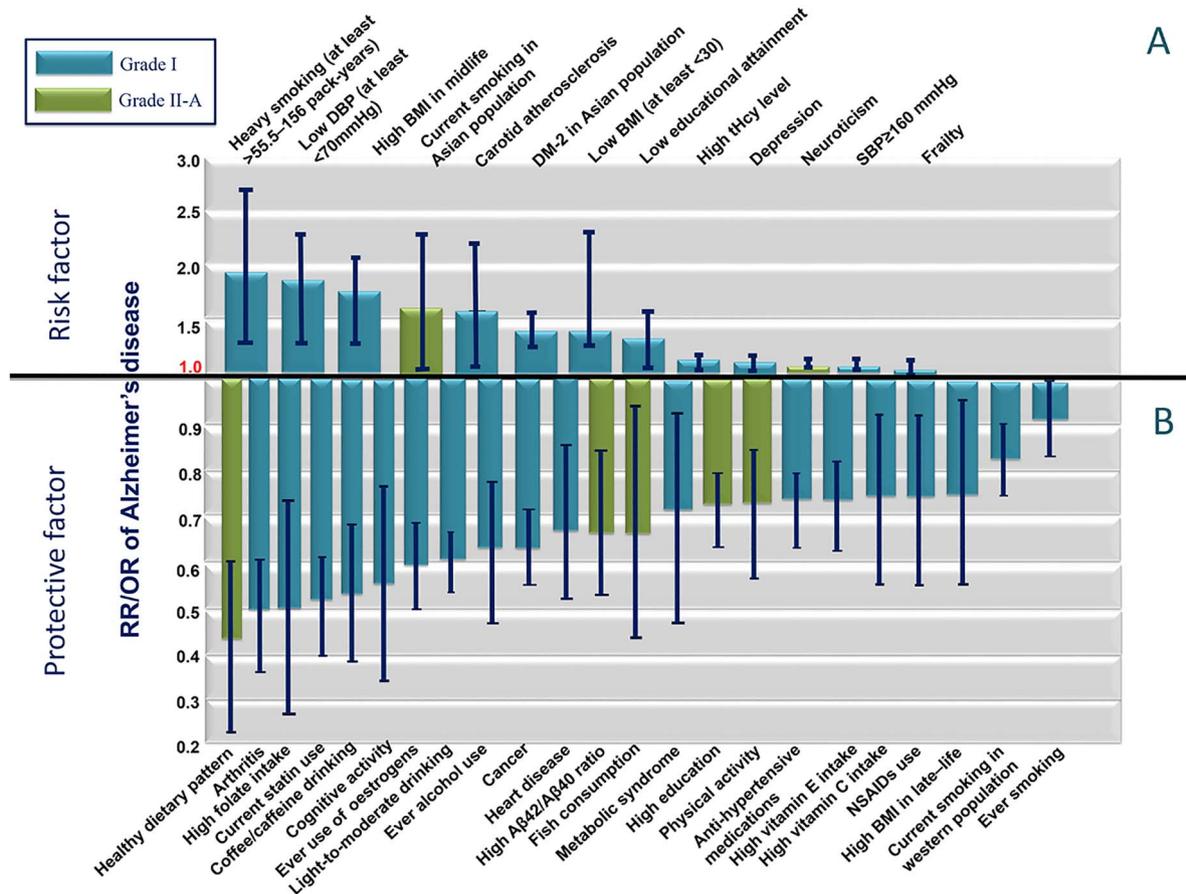


Figure 2 Factors showing significant positive (A) and negative (B) association with AD. With a relatively large pooled population (n>5000), (A) a total of 13 (11 with grade I evidence and 2 with grade II-A evidence) factors showed a trend of increasing risk of AD while (B) a total of 23 (18 with grade I evidence and 5 with grade II-A evidence) factors showed a trend of decreasing risk of AD. The height of the strip is representative of the effect size. The length of the longitudinal line is representative of the range of 95% CI (AD, Alzheimer’s disease; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; NSAIDs, non-steroidal anti-inflammatory drugs; RR, relative risk; SBP, systolic blood pressure; tHcy, total homocysteine).

potential dose–response relation between BMI in mid-life and AD risk (see online supplementary table e-5A). For low educational attainment, adjusting heterogeneity leads to a similar effect (RR=1.30, 95% CI 1.15 to 1.45). Results from subgroup analysis suggested that education ≤6–8 years (grade II-A, RR=1.58) showed a greater risk than education ≤10–16 years (grade I, RR=1.35), indicating a potential dose–response relation between low education and AD risk (see online supplementary table e-5A). For depression, the heterogeneity was reduced to 30.3% and the pooled effect was mildly elevated (RR from 1.08 to 1.18) when one single study which did not report specific criteria for AD was excluded (see online supplementary table e-5A).

For healthy dietary pattern and high participation in cognitive activity, subgroups analysis showed nearly unchanged results (see online supplementary table e-6A). For fish consumption (grade I) and anticipation in leisure-time physical activity (grade II-A), high frequency showed a higher trend for reducing AD risk than the total amount or duration (see online supplementary table e-6A). For the association between high education and AD, the heterogeneity cannot be further explained, maybe due to different definition for years of high education. The less strong evidence (grade II) via subgroup analysis for each year increase in education showed no significant association with the disease (see online supplementary table e-6A). For NSAIDs use, ‘heavy versus none’ use exhibited a higher risk (grade II-B,

RR=0.38, I²=32.6%) than ‘yes versus no’ use (grade I, RR=0.64, I²=30.9%). Non-aspirin NSAIDs use showed a significant trend of protecting AD (grade II-B, RR=0.54, 95% CI 0.39 to 0.69) while ‘any NSAIDs use’ did not show any significant association (grade II-A) (see online supplementary table e-6A). For higher BMI in late life, subgroup analysis based on the study design type leads to a reduced heterogeneity (see online supplementary table e-6A). For alcohol consumption, alcohol intake (especially 1–3 drinks per day but not alcoholism) showed a protective trend (grade I, see online supplementary tables e-6A and e-7A).

For the factors which primarily showed no significant associations, we further found positive associations of AD with heavy smoking (at least >55.5–156 pack-years, grade I), high systolic blood pressure (SBP≥160 mm Hg, grade I), low BMI (at least <30 kg/m², grade I), low DBP (at least <70 mm Hg, grade I), current smoking in the Asian population (grade II-A), history of stress and DM-2 in the Asian population (see online supplementary table e-7A). Also, we found negative associations of AD with current smoking in the Western population (grade I) (see online supplementary table e-7A, figure 2).

Assessment of publication bias

On the basis of results from the Egger test, there was evidence of publication bias for 10 factors (see online supplementary

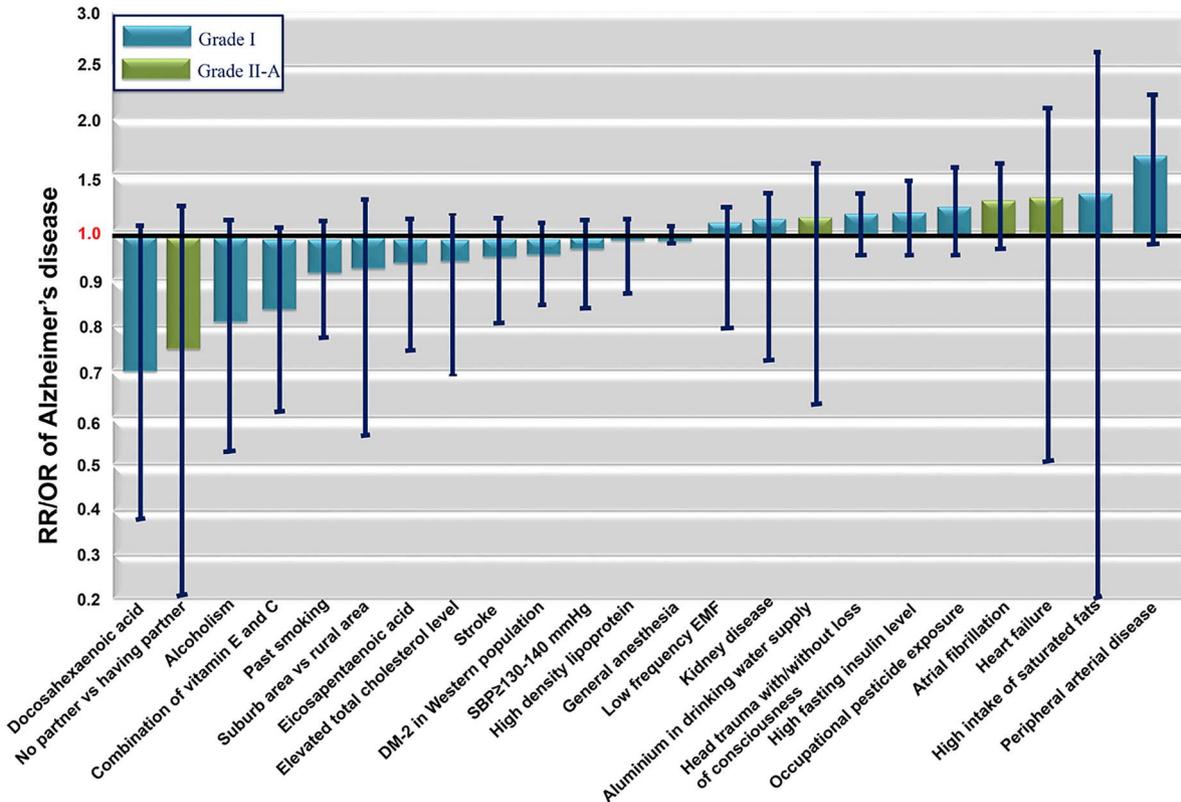
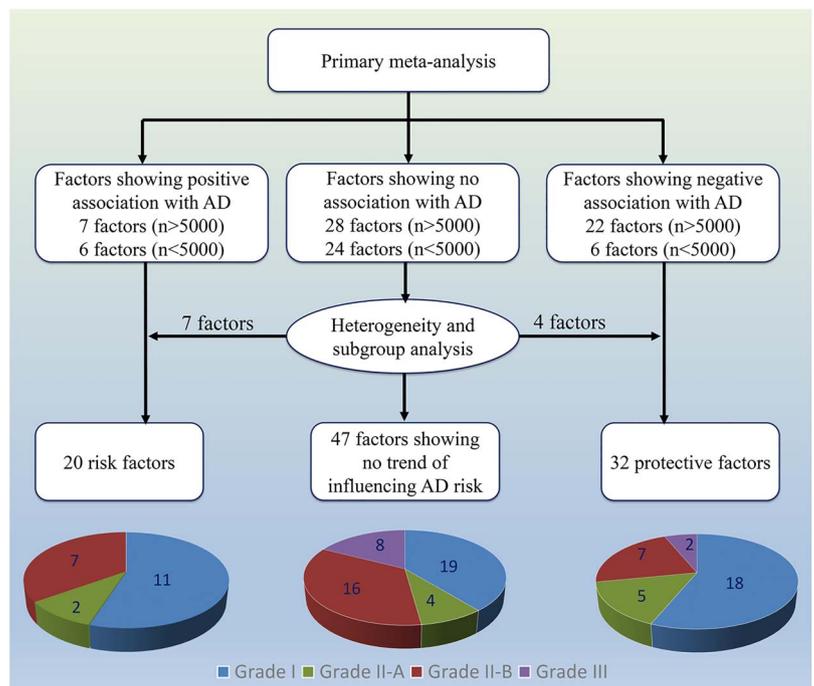


Figure 3 Factors showing no significant association with AD. With a relatively large pooled population ($n > 5000$), a total of 23 (19 with grade I evidence and 4 with grade II-A evidence) factors showed no significant association with AD risk. The height of the strip is representative of the effect size. The length of the longitudinal line is representative of the range of 95% CI (AD, Alzheimer's disease; DM, diabetes mellitus; EMF, electromagnetic field; RR, relative risk; SBP, systolic blood pressure).

table e-2). Using the trim and fill method to account for the bias barely had an effect on the summary estimate for personality (neuroticism) and depression, but did influence the summary estimate for high educational attainment (RR from 0.721 to 0.830, 95% CI 0.777 to 0.887), stress (RR from 1.680 to

1.452, 95% CI 0.963 to 2.191), high serum total homocysteine (tHcy) levels (RR from 1.140 to 1.155, 95% CI 1.088 to 1.226), high serum total cholesterol level (RR from 0.961 to 1.071, 95% CI 0.898 to 1.279), docosahexaenoic acid (DHA) consumption (RR from 0.700 to 0.758, 95% CI 0.517 to

Figure 4 Selection procedure and evidence grade of factors associated with Alzheimer's disease (AD) risk. The primary meta-analysis identified 93 factors with >5000 or <5000 pooled population. After further heterogeneity and subgroup analysis, a total of 20 risk factor and 30 protective factors with heterogeneous grade of evidence were identified. The evidence grade for risk factor was I (11), II-A (2), II-B (7), III (0); the evidence grade for protective factors was I (18), II-A (5), II-B (5), III (1); the evidence grade for factors showing no significant association was I (19), II-A (4), II-B (16) and III (8).



1.112), low educational attainment (RR from 1.410 to 1.595, 95% CI 1.315 to 1.935), heavy smoking (RR from 1.400 to 1.641, 95% CI 1.008 to 2.670), and high participation in cognitive activity (RR from 0.570 to 0.582, 95% CI 0.452 to 0.749). However, their adjusted statistical meanings are hardly altered.

Population attributable risk

Among 13 risk factors showing significantly positive associations (grade I and II-A, see [figure 2](#)) with AD in our meta-analysis, a total of 9 risk factors for which global prevalence was accessible were selected for calculation (see online supplementary table e-8). Among these factors, we take the largest study for hyperhomocysteine as a means to obtain a proxy of global exposure.¹² The prevalence was found as follows: obesity (3.4%),¹³ current smoking in the Asian population (34.7–61.1% for men and 0.5–2.6% for women),¹⁴ carotid atherosclerosis (25.4% for men and 26.4% for women),¹⁵ DM-2 in the Asian population (8.2%),¹⁶ low education (\leq primary school; 40%),³ hyperhomocysteine (27.5%),¹² depression (13.2%),³ hypertension (8.9%)³ and frailty (4.9–27.3%).¹⁷ The PAR of these modifiable risk factors varied from 0.175% to 24.5% (see online supplementary table e-8). The combined PAR indicated that these nine potentially modifiable risk factors contribute to up to roughly 66% of AD cases globally (see online supplementary table e-8).

DISCUSSION

More than 116 individual risk factors as potential targets for strategic intervention were found, of which 93 had data eligible for meta-analysis. With a relatively larger pooled population (>5000, grade I and II-A evidence), 37/50 factors significantly altered risk of future AD occurrence and 22/46 factors did not reach significance ([figure 4](#)). Identified factors can be roughly categorised into seven groups, as discussed below. Among them, we found grade I evidence for most factors ([figure 2](#)), and grade II-A evidence for seven factors, including neuroticism, high A β 42/40, high fish consumption, healthy dietary pattern, high education, more physical activity and current smoking in Asian population ([figure 2](#)).

Seven groups of modifiable risk factors

Pre-existing disease

The poor overall health status such as frailty (grade I, [figure 2](#), see online supplementary table e-5A), dysfunctional gait speed and poor self-rated health status (reported by single studies in online supplementary table e-3) may to some extent be suggestive of the mild risk of developing AD. A history of cancer is associated with AD risk reduction by approximately 37% (grade I, [figure 2](#), see online supplementary table e-6A). The contradictory pathophysiological process of these two conditions (degeneration vs replication) may underlie this association. Grade II-B evidence indicated that low bone mineral density (osteoporosis) showed a significant elevation in AD risk (RR=2.07, 95% CI 1.22 to 2.92), suggesting that the Ca²⁺ ion may play a role in AD occurrence (see online supplementary table e-5B), consistent with the single findings that high exposure to the sun at midday and high intake of vitamin D can lend protection from subsequent AD (see online supplementary table e-3).

Numerous studies have linked various cardiovascular factors with AD risk.¹⁸ In the present meta-analysis, carotid atherosclerosis showed trends of increasing risk of the disease (grade I, [figure 2](#), see online supplementary table e-5A). As we know, higher arterial stiffness is associated with higher SBP, increased pulse pressure and atherosclerosis.¹⁹ Accordingly, we found grade I evidence supporting a positive association between AD

risk and high SBP (\geq 160 mm Hg) (see online supplementary table e-7A). On the other hand, it seemed that hypertension and hypotension will increase risk of AD occurrence. Results from single studies indicated a positive association with low pulse pressure and a history of myocardial infarction (see online supplementary table e-3), which is validated by grade I evidence for low DBP (RR=1.87, 95% CI 1.36 to 2.37) in our meta-analysis ([figure 2](#), see online supplementary table e-7A). However, the hypothesis of low cerebral perfusion did not get fully validated since that heart disease and history of stroke (both were grade I evidence) showed a negative or no association with AD risk ([figure 2](#), see online supplementary table e-6A). This result for stroke is in contrast to a recent meta-analysis which included seven cohort studies and two case-control studies and reported positive association,²⁰ a larger population (11 cohort and 5 case-control studies) in our analysis may be the reason for the difference.

Previous studies found a positive association of AD with a history of DM-2,²¹ which is consistent with our results from cohort studies (RR=1.33; 95% CI 1.14 to 1.52), although it was not found to significantly alter risk (however with a high heterogeneity=83.1%) in our primary analysis combining cohort and case-control studies. We suspect that the absent association was due to high heterogeneity arising from the case-control design. The subgroup analysis showed a positive association between AD risk and DM-2 in the Asian population (grade I, but no association in the Western population) ([figure 2](#), see online supplementary table e-7A). On the other hand, MS showed a trend of reducing AD risk by roughly 29% (grade I), suggesting that biochemical exposures in serum may play important roles in affecting risk of the disease, which will be discussed below.

Biochemical exposures in serum/plasma

Multiple cardiovascular conditions have been linked to vascular dementia as well as to AD risk, and the hyperhomocysteinemia (tHcy) is a recognised risk factor for vascular disorders. We identified grade I evidence showing that a high tHcy level in serum can add up a mild but significant risk of subsequent AD ([figure 2](#), see online supplementary table e-5A). Given that tHcy, folate and vitamin B12 are all involved in methylation reactions which are necessary for monoamine neurotransmitters, phospholipids, and nucleotides production,²² it can be deduced that these three special chemicals are all related to AD risk, which is partly validated by the meta-analysis results (see online supplementary table e-6A).

Despite the negative association of MS with AD incidence ([figure 2](#), see online supplementary table e-6A), we failed to find any association for high total cholesterol level (high-density lipoprotein) and fasting insulin level even after adjusting for heterogeneity (see online supplementary table e-7A). Additionally, a significant association of high plasma A β 40 level (but not A β 42) with AD risk was reported (see online supplementary table e-3). Similarly, a high A- β 42/40 ratio reduced AD risk by about 31% (grade II-A, [figure 2](#), see online supplementary table e-6A), indicating that the plasma A β 40 level may contribute to AD incidence more than A β 42, in spite of different voice.²³

Dietary exposures

Consistent with the negative association for a high serum folate level, grade I evidence showed that a high intake of folate reduces the risk by roughly 49% ([figure 2](#), see online supplementary table e-6A). Mounting evidence showed that oxidative stress is of importance in AD pathophysiology,²⁴ and therefore great attention has been focused on the antioxidants (such as

vitamin E and C) in preventing AD occurrence.²⁵ In the present meta-analysis, either a high vitamin E or C intake showed a trend of attenuating risk by about 26% (grade I, see online supplementary table e-6A). Surprisingly, we failed to prove significant association with the intake of both these antioxidants in combination (RR=0.82; 95% CI 0.60 to 1.04).

In addition to the short-term effect of coffee/caffeine on stimulating the central nervous system, its long-term favourable influences in preventing AD (46%) have been validated in our meta-analysis (grade I, figure 2, see online supplementary table e-6A). Otherwise, although we failed to find any association with DHA, eicosapentaenoic (EPA), ω 3 fatty acid and saturated fats intake (possibly for the relatively small pooled population) (see online supplementary table e-6), fish consumption with a larger pooled population (n=23 510) exhibited a trend of weakening risk by 31% (grade II-A, figure 2, see online supplementary table e-6A). Also, we found grade I evidence supporting that more frequent consumption of fish will cut the risk by 36%. Similarly, the healthy dietary pattern (such as a Mediterranean-type diet) reduces AD risk by about 57% (grade II-A, figure 2, see online supplementary table e-6A). Otherwise, although the hypothesis of a link between aluminium/silicon and AD has long been emphasised,²⁶ we did not identify any significant association, possibly due to non-uniform approaches to quantifying the exposures (see online supplementary table e-7A for aluminium and table e-7B for silicon).

Medical exposures: drugs or therapy

Grade I evidence supported a protective role of oestrogen in reducing AD risk (by approximately 40%), emphasising the favourable role of the exogenous hormone in preventing AD incidence (figure 2, see online supplementary table e-6A). Otherwise, the results in our analysis were supportive of roles of neuroinflammation in AD occurrence.²⁷ We found grade I evidence for NSAIDs use with a trend of reducing AD risk by about 26% (figure 2, see online supplementary table e-6A). Single evidence was also reported that high-sensitivity C reactive protein levels at mid-life would increase AD risk (RR=2.3, 95% CI 1.0 to 5.4)²⁸ (see online supplementary table e-3). Grade II-B evidence indicated dose-dependent protective effect of NSAIDs (see online supplementary table e-6A). On the other hand, current and longer use (but not ever use) of statin drugs showed separately 48% and 76% reduction in AD risk, potentially suggesting a protective role of statin in a dose-dependent way (grade I, see online supplementary table e-6A).

Lifestyle

As the most commonly used proxy of cognitive reserve (CR), educational attainment has been widely investigated in preventing AD. Our result showed a mild but significant positive association with low educational attainment (grade I, figure 2, see online supplementary table e-5A) and negative association with high educational attainment (grade II-A, figure 2, see online supplementary table e-6A). Specifically, education level \leq 6–8 years (grade II-A) showed more risk in influencing AD incidence than education level \leq 10–16 years (grade I), suggesting the potential presence of a dose–response relation.²⁹ Additionally, all other CR proxies, including physical activity, cognitive activity and socioeconomic status, showed trends of lowering risk of AD in the meta-analysis (28%, 13% and 43% separately). The outcome is similar after adjusting for heterogeneity (see online supplementary table e-6A). Additionally, we failed to identify any significant association of AD risk with ever, past or current smoking in the primary analysis (grade I, see online supplementary table e-6A and table e-7A).

Nonetheless, the pooled results of cohort studies for current smoking showed a positive association with AD risk (see online supplementary table e-7A). Further, in the subgroup analysis, we found totally opposite but significant associations of current smoking in different populations. Specifically, current smoking renders protection from AD in the Western population (grade I) while it increases risk in the Asian population (grade II-A) (see online supplementary table e-7A). After adjusting for heterogeneity, we found grade I evidence showing that heavy smoking (at least >55.5–156 pack-years) would increase the risk of developing AD (figure 2, see online supplementary table e-7A).

On the other hand, grade I evidence indicated that ever alcohol use (RR=0.63) as well as light-to-moderate drinking (1–3 drinks per day) (RR=0.61) showed decreasing trends in affecting AD risk (figure 2, see online supplementary table e-6A) while high alcohol consumption (alcoholism) showed no significant association (figure 3, see online supplementary table e-7A). Although some evidence (grade II-B) showed that residence in rural areas reduced risk by roughly 30% (see online supplementary table e-6B) and a single study reported that well water drinking doubles the risk (see online supplementary table e-3), residence in suburb areas with grade II-A evidence indicated no influence on AD risk (see online supplementary table e-7A). Moreover, grade I evidence indicated that influences of BMI on AD risk are complex and depend on age: high BMI in mid-life would increase the risk of the disease while high BMI in late life would be protective (figure 2). The outcome is similar after adjusting for heterogeneity. Also, we found grade I evidence showing that low BMI (at least <30 kg/m²) would increase AD risk (figure 2, see online supplementary table e-7A). A history of stress was found to be a risk factor for AD in our analysis (grade II-B, RR=2.03, 95% CI 1.48 to 2.57).

Occupational exposure

Although association with grade II-B evidence was found for one specific pesticide (dieldrin) level in serum, the pooled population is quite small (n=310; see online supplementary table e-7B) and we did not find any significant associations with four occupational exposures including low frequency electromagnetic field, solvent, pesticide and aluminium, possibly due to different measuring approaches for exposures (see online supplementary table e-7A and e-7B).

Psychological conditions

The pooled population in the present analysis is relatively small for personality which is composed of five components, of which only neuroticism (grade II-A, positive) and conscientiousness (grade II-B, negative) were found to have a mild association with AD (see online supplementary table e-5A and table e-7B). However, a very recent cohort meta-analysis combined with a novel cohort study with a larger pooled population (n=5054; we mentioned this study independently as it was published after our searching deadline) also indicated significant association of AD risk with neuroticism and conscientiousness.³⁰ On the other hand, depression is believed to be a critically important health issue in old age. In our meta-analysis, depression showed a slight increase in AD risk (grade I, see online supplementary table e-5A), probably because patients with depression are inclined to do less physical activity, cognitive activity and have less purpose in life, which are all correlated with AD risk.³¹

Limitations of the analysis

First, we restricted the scope of our search to English articles from specific databases. We thus adjusted the publication bias

via Stata software, as a compensatory measure. Second, not all studies made enough adjustment for confounders. Third, we only included epidemiological researches but not clinical trials, especially for some factors such as antihypertensive drugs, statins or antidiabetic drugs. Fourth, the different categorisation of exposure level employed in different studies constrained us from accurately describing the risk factor in a quantitative manner. We ignored the dose effect, type and timing of drugs and instead chose the semiquantitative description (such as high, heavy, low) for some risk factors. Our attempts to address it in the subgroup analysis were not enough and the dose–response meta-analysis and clinical trials were anticipated. Fifth, the number of pooled populations used in some analyses is relatively small for some risk factors (especially for factors with grade II-B and III evidence), which should be interpreted with caution.

Statistically significant heterogeneity was found in some (29/93) of the meta-analyses performed. This is expected, because of the differences between individual studies in, for instance, case ascertainment, study population characteristics, exposure measurement, age and gender stratification, and whether crude or adjusted risk estimates were reported. We have made further analyses according to characteristics of studies and adjusted the heterogeneity as much as we could (see online supplementary table e-4).

CONCLUSION

This is the first comprehensive systematic review and meta-analysis which takes into account almost all risk factors for AD suitable to be intervened via personal, clinical and public strategy. The current meta-analysis emphasised the heterogeneity of modifiable risk factors of AD and the complexity of its aetiology, and indicated that the effective interventions in diet, medications, biochemical exposures, psychological condition, pre-existing disease and lifestyle may be promising options for preventative strategies. Further good-quality cohort studies and randomised controlled trials targeting these elements are necessary.

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

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