Modifiable Risk Factors for Incident Dementia and Cognitive Impairment: An Umbrella Review of Evidence

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Abstract

Dementia and cognitive impairment can be attributed to both genetic and modifiable risk factors. Recently, considerable evidence emerged and urgently require standardized evaluation. To address it, we conducted an umbrella review of prospective studies regarding the associations of dementia and cognitive impairment with modifiable factors to evaluate the strength and validity of the existing evidence. We searched PubMed, Embase, CINAHL and Cochrane Database of Systematic Reviews to identify relevant systematic reviews and meta-analyses of prospective studies. Mendelian randomization studies were reviewed to assess the causality for these associations. For each association, we analyzed the summary effect size, 95% confidence interval, 95% prediction interval, heterogeneity, small study effect and excess significance bias. Based on these estimates, the evidence was graded into levels of convincing, highly suggestive, suggestive, or weak. In total, 12015 articles were identified, of which 118 eligible studies yielded 243 unique associations. Convincing evidence was found for associations of dementia and cognitive impairment with early-life education, midlife to late-life plasma glucose, body mass index, atrial fibrillation, benzodiazepine use, and gait speed. Suggestive to highly suggestive evidence was found for associations of dementia and cognitive impairment with midlife to late-life blood pressure, homocysteine, cerebrovascular diseases, hearing impairment, respiratory illness, anemia, smoking, alcohol consumption, diet, sleep, physical activity and social engagement. Among convincing evidence, Mendelian randomization studies verified genetic predicted causal relationships for education and plasma glucose with Alzheimer's disease. Modifiable factors identified in this study, especially those with high-level evidence, should be considered in dementia prevention.

Trial registration: PROSPERO CRD42020195729.

Introduction

As population aging and life expectancy extends, over 50 million people worldwide suffer with dementia and the number will triple to 152 million by 2050 [1]. The high prevalence of dementia brings heavy financial and caring burden to families and society. The estimated global cost of dementia in 2018 is US$1 trillion and the figure will rise to US$ 2 trillion by 2030 if it’s not properly prevented or treated [1]. 75% of caregivers feel stressed between caring dementia patients and meeting other responsibilities [2]. There is only one controversial disease-modifying drug, aducanumab[3], for Alzheimer's dementia (AD) while no therapies to delay the onset or progression of other types of dementia yet, largely because of complicated gene-environment interactions and unclear pathophysiological mechanisms which make it difficult to perform targeted drug development. The dilemma of high disease burden while no effective treatment emphasizes the necessity for primary prevention.

Promisingly, some studies have reported downwards trend of dementia [4], probably results from higher education and/or better vascular risk factors management [5, 6]. The Lancet Commission indicated that modifiable factors accounting for around 40% dementia worldwide, including education, hypertension, diabetes, obesity, depression, hearing impairment, brain injury, physical inactivity, social isolation,

smoking, alcohol consumption and air pollution [7, 8]. Modification of the factors has been suggested in dementia prevention. In earlier report, we proposed 21 suggestions for AD prevention targeting modifiable factors [9]. Nevertheless, hierarchies of evidence have not been determined across various factors, and problems of different study designs, between-study heterogeneity may bias the results.

To address the issue, we performed an umbrella review of existing evidence to identify the compelling associations of modifiable factors throughout the life course with incident dementia and cognitive impairment. We focused on evaluating the strength and validity of available associations then identified the factors with high-level evidence, which should provide perspectives for dementia prevention.

Methods

The umbrella review was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidance [10] (S1 Table), as well as standardized methods and principles of umbrella reviews [11,12]. It was registered with PROSPERO, number CRD42020195729.

Search strategy

We searched PubMed, Embase, CINAHL, and Cochrane Database of Systematic Reviews from inception to July 31, 2020 using the terms (dementia OR Alzheimer OR Alzheimer's OR cognitive impairment OR cognitive decline OR cognitive dysfunction) AND (systematic review OR meta-analysis OR Mendelian randomization) (S2 Text). No restrictions or filters were applied in the search strategy. We also manually searched the cited references of the included articles.

Selection criteria

Eligible articles were included if they were systematic reviews and meta-analyses of randomized controlled trials (RCTs) or observational prospective studies (OPSs), Mendelian randomization (MR) studies examining associations of modifiable factors with incident dementia and cognitive impairment. All-cause dementia (ACD) including AD, vascular dementia (VD) and any other types of dementia, cognitive impairment (CI) and cognitive decline (CD) were all considered. The articles specifically recruited participants with known dementia at baseline were excluded. When multiple reviews on the same association were identified we chose the one with the most recent and the largest number of primary studies to avoid duplication. If the most recent review is not at the same time the largest one, we explore the reason for the discrepancy. If the most recent review includes more prospective studies while the largest one not, we kept the most recent one, otherwise we kept the largest one. Articles containing non-OPSs studies but conducting the subgroup analysis of OPSs were included. Articles including less than three component studies were excluded. Only English written articles permitting easy access to the source information were included.

Data extraction

Three investigators (YN Ou, Y Qu, KM Wu) independently retained eligible articles by scanning the titles and abstracts then reviewing the full-text. Any disagreement was resolved by consensus and arbitration. For each eligible meta-analysis, we extracted PMID/DOI, first author, publication year, journal name, sources of funding, number of included studies, number of total cases and participants, exposure, outcome, summary effect sizes along with their corresponding 95% confidence interval (CI), any measure of heterogeneity and publication bias. For each primary study, we extracted first author, publication year, number of cases and participants, effect sizes and CI. For each MR study, we extracted data on PMID/DOI, first author, publication year, journal name, number of total cases and participants, exposure, outcome, genetic instruments, MR causal effect estimates and CI.

Quality appraisal

For included systematic reviews and meta-analyses, the methodological quality was assessed with A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) [13]. AMSTAR 2 includes 16 items, seven of which can critically affect the validity of a review and its conclusions so that regarded as critical domains. The methodological quality is rated as high, moderate, low and critically low depending on weaknesses in critical and/or non-critical items.

Statistical analysis

For each association, we calculated the summary relative risk (RR) and 95% CI using random effects methods [14]. For the articles that presented results with odds ratio (OR), we transformed primary ORs to RRs using the algorithm: $RR = OR / [(1 - p_0) + (p_0 \times OR)]$ (p_0 indicates the incidence of endpoint in non-exposed group of the cohort) [15]. A 95% prediction interval (PI) was calculated to better evaluate the precision of the result. The heterogeneity was assessed by I^2 statistic [16] and it is considered large when $I^2 > 50\%$.

We examined whether smaller studies gave greater side effects estimates than larger studies by Egger's regression asymmetry test [17]. $p<0.10$ was taken as statistical evidence of the small study effects.

We evaluated whether there was a relative excess bias of significant findings in the published literature by excess statistical significance test [18,19], which assessed whether the observed (O) number of statistically significant studies ($p<0.05$) is too large compared with the expected (E) number using the χ^2 test. The expected number of studies was calculated by summing the statistical power estimated of each component study (assuming the true effect size the same as that of the largest component study). $p<0.10$ was taken as statistical evidence of the presence of excess significance.

Gradation of the evidence strength followed the rules[11]: convincing (class I) when random effects $p<10^{-6}$, number of cases>1000, $I^2<50\%$, 95% PI excluding the null, no small-study effects and no excess significance bias, highly suggestive (class II) when $p<10^{-6}$, number of cases>1000, largest study with a statistically significant effect and class I criteria not met, suggestive (class III) when $p<10^{-3}$, number of

cases>1000 and class I–II criteria not met, weak (class IV) when p<0.05 and class I–III criteria not met, non-significant when p>0.05.

For MR studies, we did not conduct quantitative syntheses and just present here a descriptive analysis of the individual studies. p<0.05 was taken as statistical evidence of the presence of causal relationship.

All statistical analyses were done using Stata version 12.0.

Results

Study selection and characteristics

Overall, 12015 articles were retrieved from systemic literature search and 611 articles were eligible for full-text screening (Fig 1). A total of 493 articles not meeting the inclusion criteria were excluded (S3 Table). Seventy systematic reviews and meta-analyses eligible for umbrella review (S4 Text) were comprised of 5 articles of RCTs, 64 articles of OPSs and 1 article of both RCTs and OPSs. Forty-eight MR studies containing 157 causal analyses were included.

Most of the eligible articles didn't report a prior established protocol (item 2), a list of excluded studies (item 7) or the sources of funding for primary studies (item 10), which unfortunately downgraded the initial AMSTAR 2 rating. Therefore, we performed an adjusted analysis of the reporting quality by ruling out the above three domains. The adjusted reporting quality were high (39%) in 27 articles, moderate (24%) in 17 articles, low (31%) in 22 articles and critically low (6%) in 4 articles (S5 Table).

The included systematic reviews and meta-analyses published between 2010 and 2020 (median 2018, IQR 2016-2019) yielded 243 unique associations including 35 for ACD and CI/CD, 87 for ACD, 70 for AD, 21 for VD, 8 for Parkinson's disease with dementia (PDD) and 22 for CI/CD. In 243 meta-analyses, study estimates number ranged from 3 to 31 (median 6, IQR 4-10), cases number ranged from 82 to 519247 (median 1138, IQR 486-2580) and participants sample size ranged from 266 to 12523553 (median 16067, IQR 6851-49134). Altogether 138 (57%) of 243 associations were significant (p<0.05) under the random effects model, of which 75 (31%) were $p<1 \times 10^{-3}$ and 29 (12%) were $p<1 \times 10^{-6}$.

Evidence from RCTs studies

Only 9 associations were available from RCTs (S6 Table). Two interventions (22%), antihypertensive medications in midlife to late life and nonpharmacological interventions in late life, were found significantly (p<0.05) protective of ACD and CI while the evidence was weak. Of 9 associations, none had a 95% PI excluding the null value, 4 (44%) showed large heterogeneity (I^2>50%), 2 (22%) presented small-study effects (Egger's p<0.10) and 3 (33%) were observed with excess significance bias.

Evidence from OPSs studies

We summarized 30 reported associations from OPSs for ACD and CI/CD (S7 Table). The association of one (3%) risk factor, overweight (body mass index [BMI] 23-30 Kg/m^2) (RR 0.81, 95% CI 0.75-0.88) in late life, was graded as convincing evidence (Fig 2). The association of one (3%) risk factor, high BMI (BMI>23 Kg/m^2) in late life, was graded as highly suggestive evidence. Six (20%) associations were graded as suggestive evidence covering the risk factors underweight (BMI<21 Kg/m^2) in midlife, obesity (BMI>25.5 Kg/m^2) and anemia in late life, insomnia, long nocturnal sleep duration, fruit and vegetables intake in midlife to late life. Eleven (37%) associations were graded as weak evidence. Of 30 associations, 3 (10%) had a 95% PI excluding the null value, 15 (50%) showed large heterogeneity, 4 (13%) presented small-study effects and 10 (33%) were observed with excess significance bias.

Eighty-five associations were examined in OPSs for ACD (S8 Table). Eight (9%) associations were graded as convincing evidence covering risk factors high education (RR 0.44, 95% CI 0.32-0.60) and low education (1.81, 1.59-2.06) in early life, depression (1.85, 1.67-2.04) and low gait speed (1.66, 1.43-1.92) in late life, severe hypoglycemia (1.69, 1.48-1.93), atrial fibrillation (1.34, 1.24-1.44) and benzodiazepine current (1.55, 1.31-1.83) or ever (1.49, 1.30-1.72) use in midlife to late life (Fig 3). Seven (8%) associations were graded as highly suggestive evidence covering risk factors diabetes mellitus, high homocysteine level, prevalent stroke, incident stroke, hearing impairment, respiratory illness and current smoking in midlife to late life. Eleven (13%) associations were graded as suggestive evidence covering risk factors high systolic blood pressure (SBP) in midlife, antihypertensive medications, orthostatic hypotension, cerebral small vessel disease (CSVD) - white matter hyperintensities (WMHs), apathy, living alone and feeling loneliness in late life, high fasting plasma glucose (FPG) level, physical activity, wine consumption and ever smoking in midlife to late life. Thirty (35%) associations were graded as weak evidence. Of 85 associations, 23 (27%) had a 95% PI excluding the null value, 25 (29%) showed large heterogeneity, 11 (13%) presented small-study effects and 12 (14%) were observed with excess significance bias.

A total of 69 associations were extracted from OPSs for AD (S9 Table). Three (4%) associations were graded as convincing evidence covering risk factors low education (RR 1.78, 95% CI 1.43-2.22) in early life, depression (1.65, 1.42-1.92) in late life, high FPG level (1.13, 1.09-1.17) in midlife to late life (Fig 4). The association of one (1%) risk factor, diabetes mellitus in midlife to late life, was graded as highly suggestive evidence. Seven (10%) associations were graded as suggestive evidence covering risk factors hypertension, obesity, overweight and high BMI in midlife, antihypertensive medications in late life, statins and hearing impairment in midlife to late life. Twenty-three (33%) associations were graded as weak evidence. Of 69 associations, 4 (6%) had a 95% PI excluding the null value, 20 (29%) showed large heterogeneity, 7 (10%) presented small-study effects and 17 (25%) were observed with excess significance bias.

For VD, 21 associations were evaluated in OPSs (S10 Table). No association was graded as convincing evidence. The association of one (5%) risk factor, diabetes mellitus in midlife to late life, was graded as highly suggestive evidence. The association of one (5%) risk factor, current smoking in midlife to late life, was graded as suggestive evidence. Ten (48%) associations were graded as weak evidence. Of 21

associations, 3 (14%) had a 95% PI excluding the null value, 9 (43%) showed large heterogeneity, 5 (24%) presented small-study effects and 5 (24%) were observed with excess significance bias.

Eight associations for PDD were explored in only one OPS (S11 Table). No association was graded as convincing, highly suggestive or suggestive evidence. Four (50%) associations were graded as weak evidence. none association had a 95% PI excluding the null value, 5 (63%) showed large heterogeneity, 1 (13%) presented small-study effects and 5 (63%) were observed with excess significance bias.

Finally, 21 associations were assessed in OPSs for CI/CD (S12 Table). No association was graded as convincing evidence. The associations of two (10%) risk factors, low gait speed in late life and physical activity in midlife to late life, were graded as highly suggestive evidence. The associations of two (10%) risk factors, diabetes mellitus and hearing impairment in midlife to late life, were graded as suggestive evidence. Seven (33%) associations were graded as weak evidence. Of 21 associations, 3 (14%) had a 95% PI excluding the null value, 5 (24%) showed large heterogeneity, 3 (14%) presented small-study effects and 2 (10%) were observed with excess significance bias.

On the whole, the evidence gradation was convincing for 12 associations, highly suggestive for 12 associations and suggestive for 27 associations throughout the life course (Fig 5). In early life, education is the only, but determining, protective factor for dementia. While in midlife, blood pressure and BMI critically influence the risk of dementia and cognitive impairment. When it moves into late life, blood pressure and BMI still matter and antihypertensive medications will benefit for prevention of dementia. Late-life depression, apathy, social isolation, low gait speed, WMHs and anemia would affect the risk of dementia and cognitive impairment as well. Additionally, the incidence of dementia and cognitive impairment are related to benzodiazepine use, plasma glucose, homocysteine, atrial fibrillation, stroke, statins, hearing impairment, respiratory illness, smoking, alcohol consumption, sleep, healthy diet and physical activity in midlife to late life.

Evidence from MR studies

As for MR studies (S13 Table), genetically predicted increment of intelligence, education especially college/university completion, height, DBP (diastolic blood pressure), lipoprotein-a, cancer, rheumatoid arthritis, gut blautia and downstream product γ-aminobutyric acid (GABA), Vitamin D and Vitamin D binding protein play protective roles in AD. In contrast, elevated fasting glucose, white matter hyperintensities, periodontitis, alcohol consumption, branched-chain amino acids (isoleucine), decreased β cell function and complement C3 may increase the risk of AD.

Discussion

We provide a comprehensive overview of 243 reported associations of modifiable risk factors with incident dementia and cognitive impairment by incorporating evidence from 70 systematic reviews and meta-analyses. 51 associations were graded as suggestive to convincing evidence and 87 were graded as weak evidence. The main factors bringing down the grade of evidence were between-study

heterogeneity indicated in one-third of the meta-analyses, the limited cases number especially for VD and PDD, the presence of small-study effects or excess significance bias. Heterogeneity was mainly derived from inconsistent diagnostic criteria for dementia and cognitive impairment as well as various exposure assessment tools among primary studies.

Education is the only significant modifiable risk factor in early life and it is convincing enough for application in the practice of dementia prevention. It is thought that education enhances the tolerance to age-related brain changes, which is implicit in the concept of cognitive reserve [20]. In contrast, social isolation in late life, either living alone or feeling loneliness, would weaken the cognitive reserve [21].

Vascular risk factors in midlife to late life including atrial fibrillation, stroke, CSVD, blood pressure, plasma glucose, BMI, homocysteine, smoking and alcohol consumption were supported by suggestive to convincing evidence increasing the risk of dementia and cognitive impairment. Hypoxia and hypoperfusion due to vascular diseases can accelerate the progression of neurodegenerative pathology [22]. In contrast, late-life high BMI is convincingly protective of dementia and cognitive impairment. Such a paradox could be partly explained by increased leptin hormone secreted by the adipose tissue, which may modulate hippocampal synaptic plasticity [23]. Furthermore, late-life BMI could influence the levels of cerebrospinal fluid (CSF) core AD biomarkers, amyloid-β (Aβ) and t-tau, as well as the volumes of hippocampus and cortex [24]. Antihypertensive medications and statins can be effective in dementia prevention based on suggestive evidence, and no particular antihypertensive class is significantly related to dementia and cognitive decline. Our analysis of OPSs reveals that healthy lifestyles including physical activity and fruit and vegetables intake contribute to decrease the incidence of dementia and cognitive impairment. However, the protective effects of physical activity and unsaturated fat supplementation are not significant in meta-analyses of RCTs.

The evidence for association of depression in late life and dementia is convincing. Neuroendocrine changes, hippocampal atrophy and vascular depression hypothesis are prominent mechanisms that may link depression and dementia [25]. Nevertheless, reverse causation may exist because depression is also a prodromal symptom of dementia. The uncertainty is similar for another neuropsychiatric symptom, apathy. Is it a sign of an early stage, or an independent risk factor for dementia? The lack of studies on early life apathy and dementia leaves this question open.

Motor dysfunction is predictive of dementia occurrence especially for PDD. Low gait speed in late life convincingly increases the incidence risk of dementia although the general evidence level of motor factors is weak partially due to the small sample size and large publication bias. The shared neural networks of cognition and motor function which are modulated by both dopaminergic and non-dopaminergic transmitter systems [26] have been suggested to explain the underpinning mechanism.

Midlife to late life sleep disturbances including insomnia and long nocturnal sleep duration are responsible for the increased incidence of dementia and cognitive decline. A U-shaped association was reported between sleep duration and cognition [27]. Possible mechanisms of insufficient sleep time include inadequate glymphatic clearance pathways and vulnerable deposition of Aβ [28]. While excessive

sleep time leading to inflammation activation may also result in cognitive deterioration [29]. Benzodiazepines are widely applied for treatment of sleep disturbances, but their use is convincingly linked to increased risk of dementia. Thus, it is necessary to find alternative pharmacological or nonpharmacological interventions in sleep management for effective dementia prevention.

Additionally, comorbidities in midlife to late life including hearing impairment, respiratory illness and anemia generated a higher risk of dementia and cognitive impairment. Detailed mechanisms are not yet known. These comorbidities may impair cognition by mediating other risk factors such as hearing impairment causing social isolation, and respiratory illness and anemia inducing hypoxic ischemic brain vascular changes.

Compared with previous work of Bellou [30], we significantly updated the evidence with advanced prospective studies and further summarized MR studies to find more solid associations. In addition, cognitive impairment with no dementia was also included to achieve an early-stage prevention. The evidence hierarchy of some factors was elevated, including education, gait speed, atrial fibrillation, BMI, homocysteine, stroke, WMHs, hearing impairment, respiratory illness, sleep and smoking, etc. While it is less suggestive for associations of cancer, aluminum, infectious diseases, low-frequency electromagnetic fields and NSAIDs. We also added evidence from MR studies to identify the risk factors not affected by confounding or reverse causation.

Our study has several limitations. First, meta-analyses of RCTs are inadequate. Beneficial factors supported by e OPSs need to be further verified by RCTs. Second, studies for dementia other than AD or VD are scarce. In our umbrella review, the dementia endpoints of the included articles are mainly AD or VD even if for articles of all-cause dementia. Only one article reported the risk factors for PDD and no studies specifically focus on frontotemporal dementia, dementia with Lewy bodies or other types of dementia. Therefore, the prevention strategies based on this study may not be applicable to all types of dementia. Third, although between-study heterogeneity, small-study effects and excess significance bias were evaluated, we cannot be sure that we excluded all of the biases that are inherent to individual studies. The inconsistence of baseline participants characteristics, exposure assessment, outcome diagnostic criteria, follow-up duration and adjustment model couldn’t be fully controlled. Assessing the quality of the primary studies included in the meta-analyses is beyond the scope of an umbrella review. Fourth, we excluded the systemic reviews without quantitative analysis, so we missed some reported risk factors. Fifth, we did not establish whether the MR reports included assessment of the phenotype in relation to the polymorphisms studied in the cohorts, which might limit their validity, for example in the case of homocysteine [31]. Finally, our study was conducted on published English articles so the results can be updated by additional epidemiological studies.

Conclusions

Our study mapped the associations of incident dementia and cognitive impairment with various modifiable risk factors. We identified factors with convincing evidence including education in early life,

overweight, depression and low gait speed in late life, severe hypoglycemia, high FPG level, atrial fibrillation and benzodiazepine use in midlife to late life, among which, education and FPG are supported by MR causal analysis. In whole, our study provides evidence for modifiable risk factors that can be considered in dementia prevention strategies. However, some of the evidence is limited by study quality and heterogeneity which need to be validated in further research.

Declarations

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Competing interests

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Authors' contributions

JT Yu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. YR Zhang and W Xu designed the study and drafted the manuscript. YN Ou, Y Qu and KM Wu were responsible for acquisition of data. W Zhang and HF Wang did data analyses and E Evangelou contributed for interpretation. XN Shen and SD Chen contributed to the Figs. JT Yu, E Evangelou, AD Smith, C Zhang, L Feng, L Tan, Q Dong, L Sun, HN Zhang and QH Zhao critically revised the manuscript.

Ethics approval

This is an observational study and no ethical approval is required.

Consent to participate

Not applicable.

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Figures

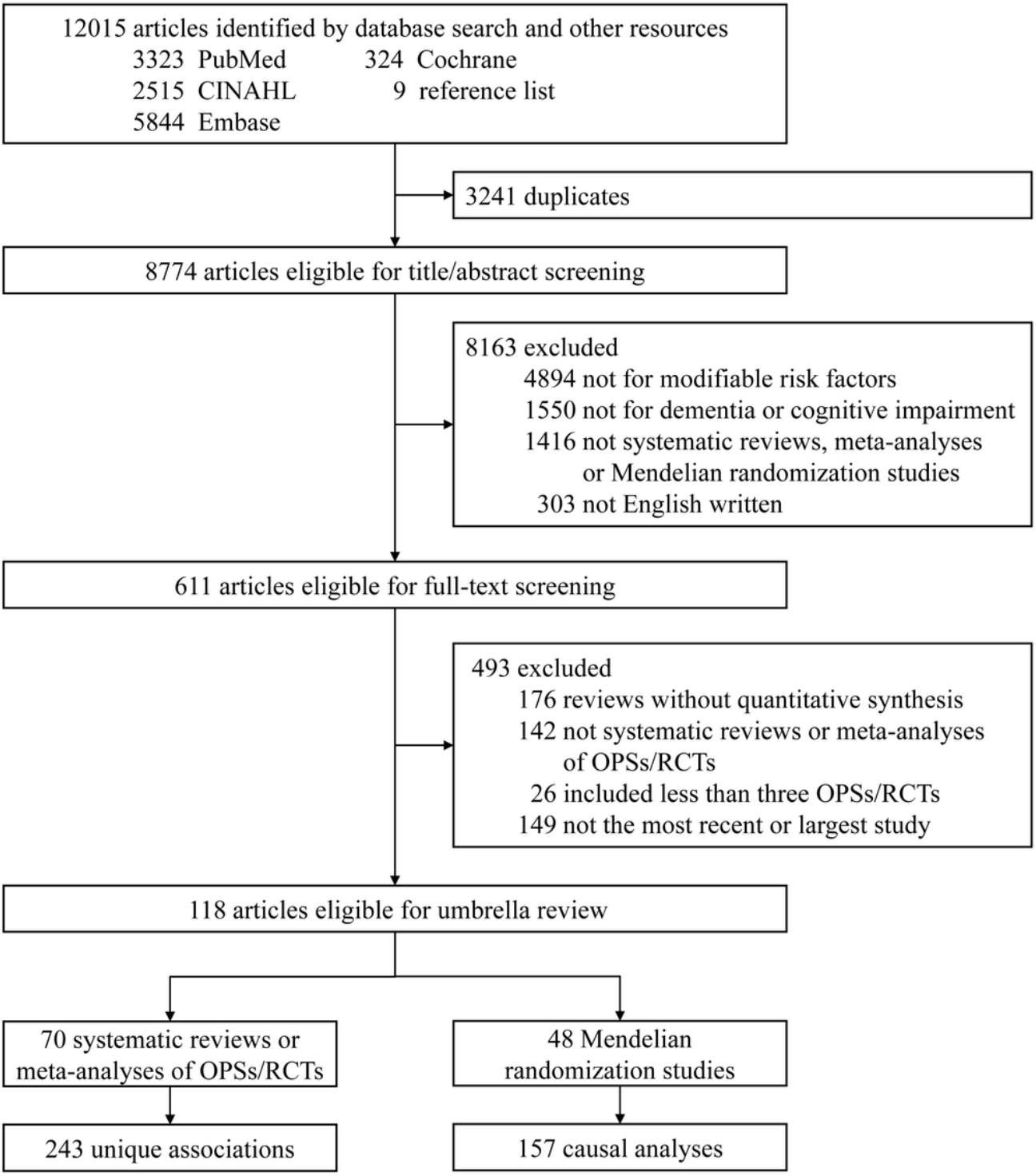

Figure 1

Flow chart of literature search. OPSs = Prospective Observational Studies, RCTs = Randomized Controlled Trials.

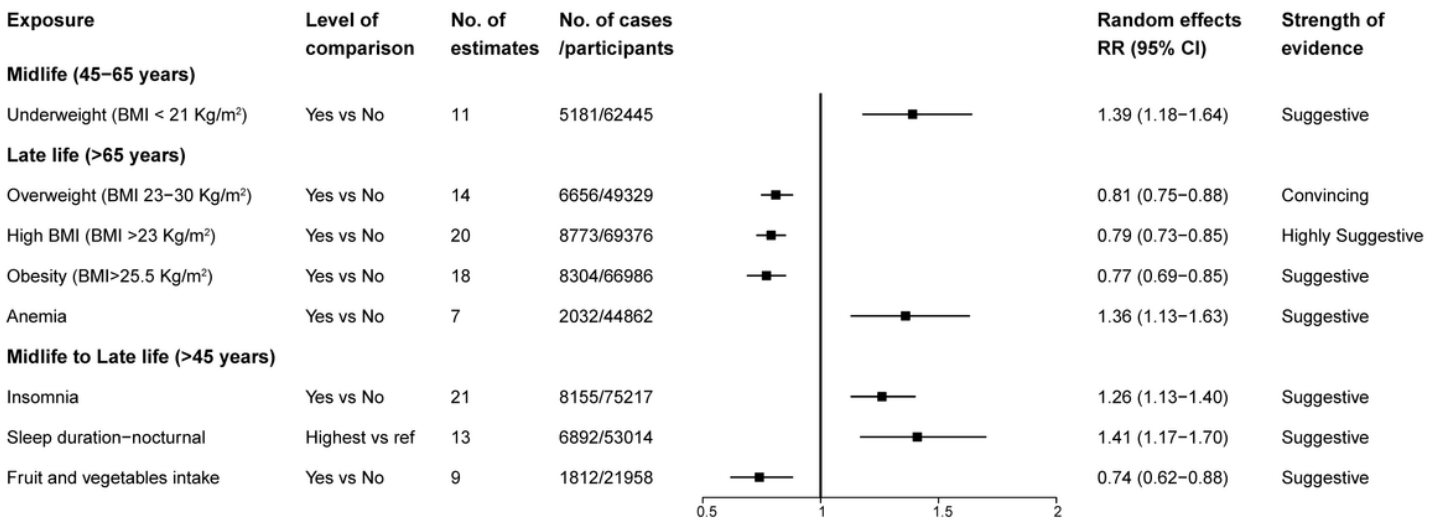

Figure 2

Characteristics and quantitative synthesis of the eligible meta-analyses of OPSs for ACD and CI/CD by life course. Only the risk factors graded as suggestive to convincing evidence were listed. Convincing evidence existed in late-life overweight. Highly suggestive evidence existed in late-life high BMI. Suggestive evidence existed in midlife underweight, late-life obesity and anemia, midlife to late-life insomnia, long nocturnal sleep duration, fruit and vegetables intake. ACD = All Cause dementia, BMI = Body Mass Index, CD = Cognitive Decline, CI = Cognitive Impairment, OPSs = Prospective Observational Studies.

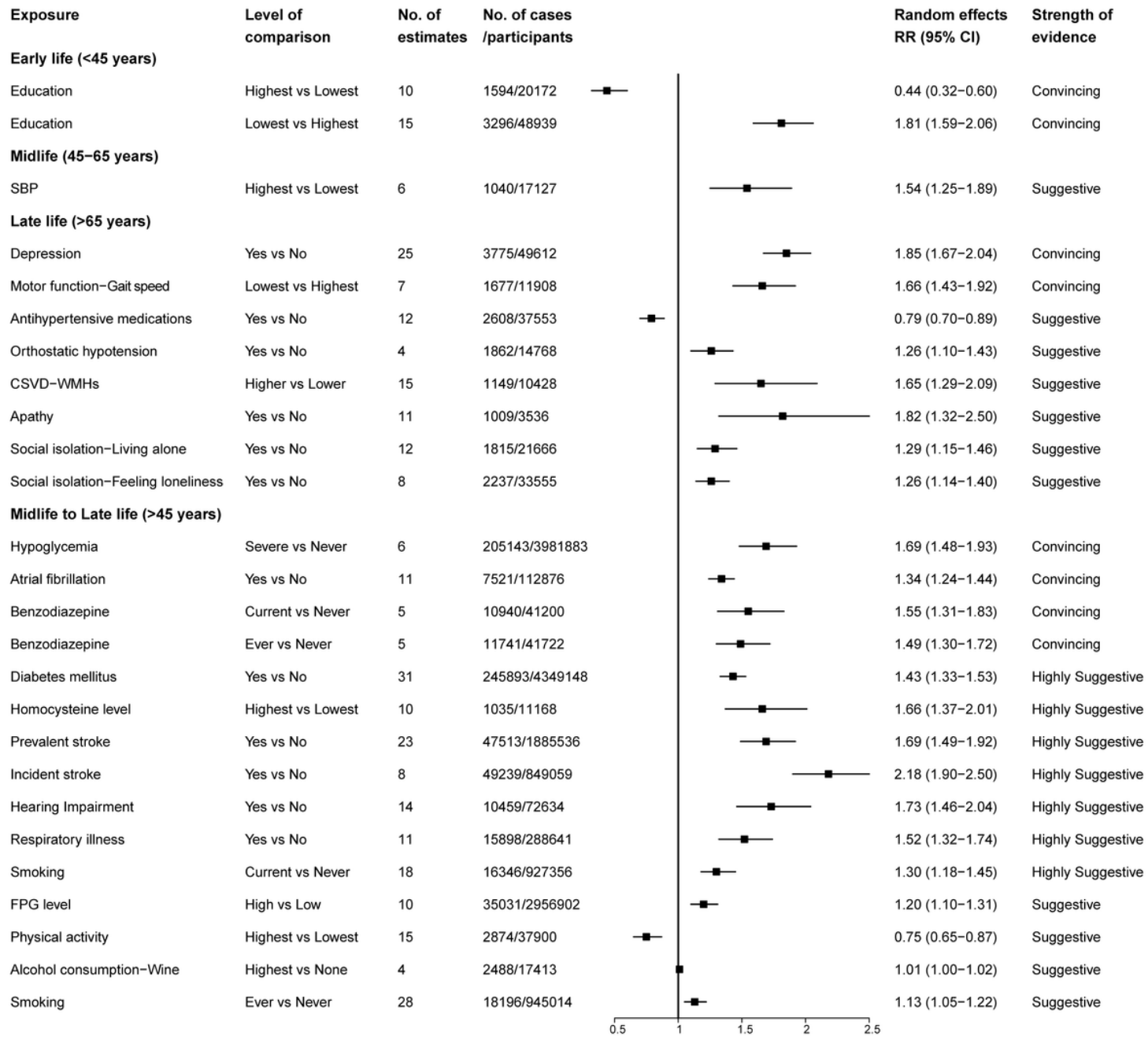

Figure 3

Characteristics and quantitative synthesis of the eligible meta-analyses of OPSs for ACD by life course. Only the risk factors graded as suggestive to convincing evidence were listed. Convincing evidence existed in early-life education, late-life depression and low gait speed, midlife to late-life severe hypoglycemia, atrial fibrillation and benzodiazepine current or ever use. Highly suggestive evidence existed in midlife to late-life diabetes mellitus, high homocysteine level, prevalent or incident stroke, hearing impairment, respiratory illness and current smoking. Suggestive evidence existed in midlife high SBP, late-life antihypertensive medications, orthostatic hypotension, CSVD-WMHs, apathy and social isolation, midlife to late-life high FPG level, physical activity, wine consumption and ever smoking. ACD = All Cause dementia, CSVD = Cerebral Small Vessel Disease, FPG = Fasting Plasma Glucose, OPSs =

Prospective Observational Studies, SBP = Systolic Blood Pressure, WMHs = White Matter Hyperintensities.

Exposure	Level of comparison	No. of estimates	No. of cases /participants	Random effects RR (95% CI)	Strength of evidence
Early life (<45 years)					
Education	Lowest vs Highest	9	1944/37954	1.78 (1.43–2.22)	Convincing
Midlife (45–65 years)					
Hypertension	Yes vs No	4	2279/866446	1.19 (1.08–1.32)	Suggestive
Obesity (BMI>25.5 Kg/m^2)	Yes vs No	6	1094/23562	2.23 (1.58–3.14)	Suggestive
Overweight (BMI 23–30 Kg/m^2)	Yes vs No	6	1094/23562	1.64 (1.24–2.18)	Suggestive
High BMI (BMI >23 Kg/m^2)	Yes vs No	7	1211/27030	1.79 (1.39–2.32)	Suggestive
Late life (>65 years)					
Depression	Yes vs No	16	1463/28746	1.65 (1.42–1.92)	Convincing
Antihypertensive medications	Yes vs No	12	3779/81651	0.81 (0.72–0.91)	Suggestive
Midlife to Late life (>45 years)					
FPG level	Highest vs Lowest	8	25286/2950748	1.13 (1.09–1.17)	Convincing
Diabetes mellitus	Yes vs No	24	46244/4587185	1.43 (1.25–1.62)	Highly Suggestive
Lipid lowering medications – statins	Yes vs No	15	9103/1192510	0.86 (0.80–0.92)	Suggestive
Hearing Impairment	Yes vs No	5	1223/11655	2.15 (1.37–3.36)	Suggestive

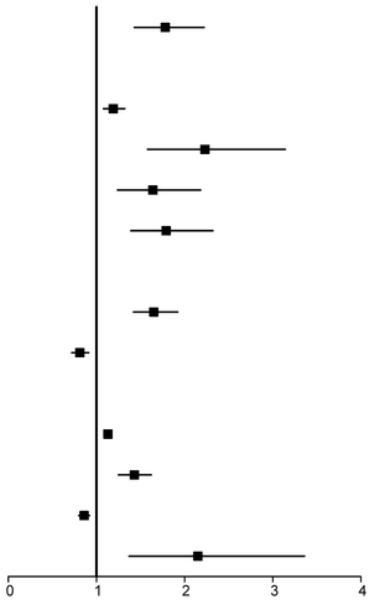

Figure 4

Characteristics and quantitative synthesis of the eligible meta-analyses of OPSs for AD by life course. Only the risk factors graded as suggestive to convincing evidence were listed. Convincing evidence existed in early-life education, late-life depression and midlife to late-life high FPG level. Highly suggestive evidence existed in midlife to late-life diabetes mellitus. Suggestive evidence existed in midlife hypertension, obesity, overweight and high BMI, late-life antihypertensive medications, midlife to late-life statins and hearing impairment. AD = Alzheimer's Disease, BMI = Body Mass Index, FPG = Fasting Plasma Glucose, OPSs = Prospective Observational Studies.

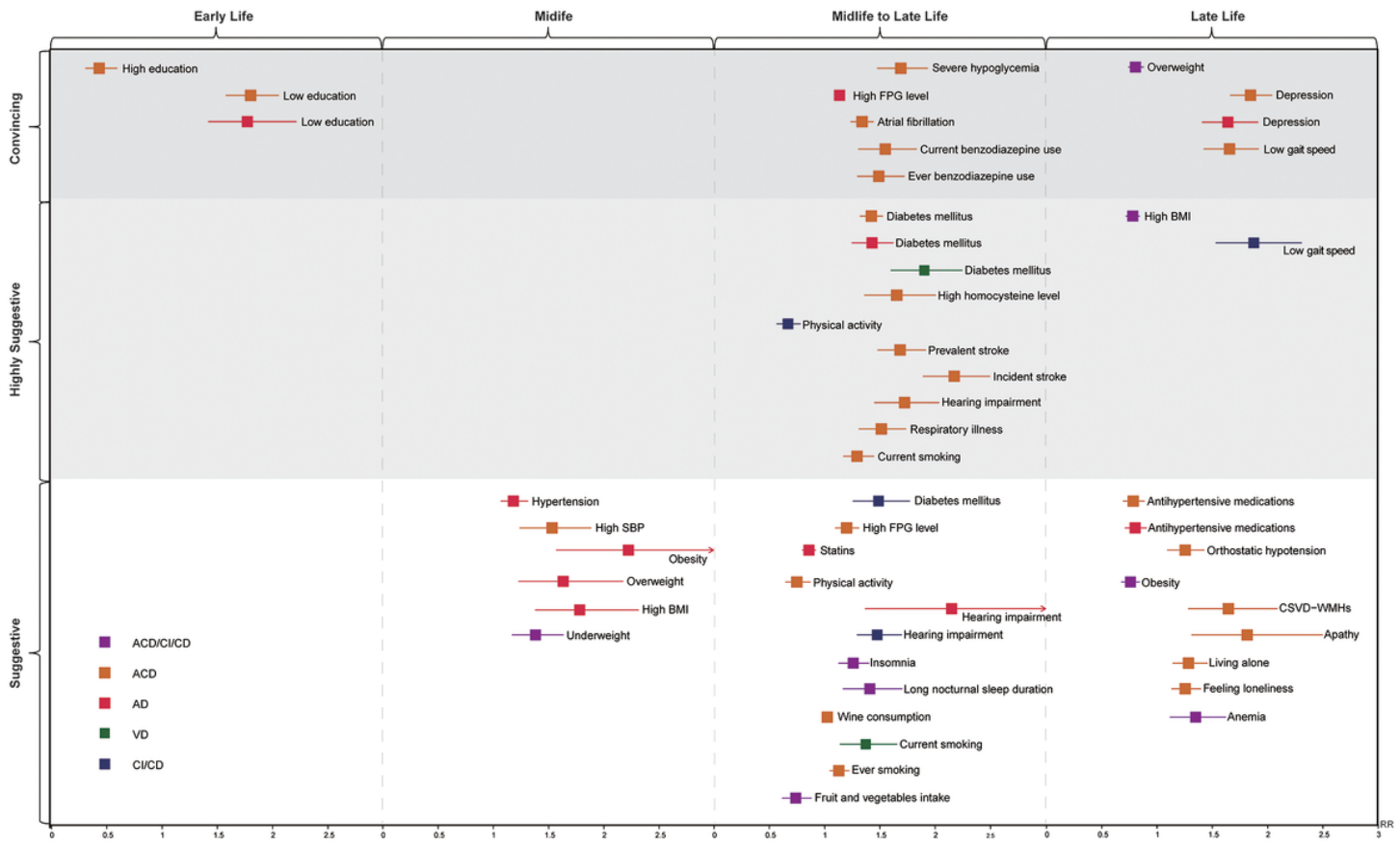

Figure 5

Distribution of modifiable risk factors graded as convincing, highly suggestive or suggestive evidence throughout the course of life. In early life, education was graded as convincing factor for dementia. In midlife, blood pressure and BMI were graded as suggestive factors for dementia and cognitive impairment. In late life, BMI, depression, low gait speed, antihypertensive medications, orthostatic hypotension, CSVD-WMHs, apathy, social isolation and anemia were graded as suggestive to convincing factors for dementia and cognitive impairment. In midlife to late life, plasma glucose, atrial fibrillation, benzodiazepine use, homocysteine, physical activity, stroke, hearing impairment, respiratory illness, smoking, statins, alcohol consumption, sleep and healthy diet were graded as suggestive to convincing factors for dementia and cognitive impairment. ACD = All Cause dementia, AD = Alzheimer's Disease, BMI = Body Mass Index, CD = Cognitive Decline, CI = Cognitive Impairment, CSVD = Cerebral Small Vessel Disease, FPG = Fasting Plasma Glucose, SBP = Systolic Blood Pressure, VD = Vascular Dementia, WMHs = White Matter Hyperintensities.

Supplementary Files

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- SupplementaryInformation.docx