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Systematic review and meta-analysis of Mendelian randomisation studies on modifiable risk factors for dementia

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Background

1 Dementia is a clinical syndrome of progressive cognitive decline and loss of everyday functioning (Chertkow *et al.*, 2013). It is caused by a variety of disease processes, most commonly Alzheimer's disease (Duong, Patel and Chang, 2017). Worldwide prevalence of dementia has nearly doubled since 1990 to 2016 due to population ageing (Nichols *et al.*, 2019). The economic burden of dementia is projected to rise significantly in the next coming decades (Wittenberg *et al.*, 2020). Studies of risk factors have identified education, physical activity, and cardiovascular risk factors (Baumgart *et al.*, 2015). Importantly, approximately a third of Alzheimer's disease cases are thought to develop from modifiable risk factors (Norton *et al.*, 2014). Although observational studies have identified risk factors in general populations, they are limited by residual confounding (for example by education) (Carlson and Morrison, 2009).

Mendelian Randomisation (MR) used genetic variants as proxy for risk factor of interest to generate estimates that are less susceptible to some types of confounding (Smith and Hemani, 2014). However, there are few primary MR studies on modifiable risk factors and dementia with differing estimates. To date, only one descriptive systematic review on dementia from MR studies has been published (Kuźma *et al.*, 2018). Therefore, we aim to perform an updated systematic review and meta-analysis of MR that will provide further insight into the causative factors of dementia.

Our protocol has been adapted from PRISMA and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines (Stroup *et al.*, 2000; Moher *et al.*, 2009). The aim of this planned meta-analysis is to:

1) Assess the causal effect of modifiable risk factors associated with dementia;
2) Quantify the effect of modifiable risk factors on the risk of dementia;
3) Provide information to guide intervention in preventing or delaying onset of dementia.

Data sources and search strategy

2 Literature search will be performed via OVID and Web of Science. These cover 13 databases: Medline, Embase, AMED, PsycINFO, BIOSIS Citation Index, Web of Science core collection, Current Contents Connect, Data Citation Index, Derwent Innovations Index, KCI-Korean Journal Database, Russian Science Citation Index, SciELO Citation Index, Zoological Record.

Following search syntaxes will be employed.
OVID:
(exp Dementia/ or exp Cognition Disorders/ or dement* or alzheimer* or cognit* or neurocognit* or ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or deficit* or complain* or disturb* or disorder* or dysfunction* or insufficien* or fail*)))
AND
(exp Mendelian Randomization Analysis/ or (Mendelian adj1 random*) or (MR not (magnetic or resonance or imag* or receptor)) or (instrumental adj1 variable*) or (genetic adj1 instrument))

Web of Science:
TS=(dement* OR Alzheimer* OR cognit* OR neurocognit* OR memory OR cerebr* OR mental*)
AND
TS=("Mendelian random*" OR "instrumental variable*" OR "genetic instrument*")

3 Articles will be selected for consideration through three stages. Uncertainties will resolved by discussion between two reviewers.

In stage 1, article relevance will be assessed from the title and abstract of the articles.
Inclusion criteria in stage 1.
- Published and pre-print primary MR studies
- Outcome of any type of dementia
- Risk factors investigating any of systolic blood pressure, diastolic blood pressure, HDL, LDL, triglycerides, total cholesterol, BMI, diabetes, or plasma glucose. If the risk factors were not explicitly mentioned in title or abstract, these studies were tentatively included for Stage 2 assessment.
Exclusion criteria in stage 1.
- Non-English articles
- Duplicates
- Unavailable full texts

In stage 2, relevance will be further assessed by reading the full texts. Full texts will be accessed through an institutional library
Inclusion criteria in stage 2.
- Risk factors investigating any of systolic blood pressure, diastolic blood pressure, HDL, LDL, triglycerides, total cholesterol, BMI, diabetes, or plasma glucose.
- Reported causal estimate value of either odds ratio, hazard ratio, relative risk or beta coefficient using inverse-variance weighted method in either main text or supplementary material.
- Reported value of either standard deviation, standard error, or 95% confidence interval in either main text or supplementary material.

In stage 3, forward searching will be performed from the selected studies to identify additional studies. Newly added studies will be processed as per stage 1 and 2.

Quality assessment

4 Quality assessment questionnaire was developed through synthesizing three published guidelines (Davies, Holmes and Davey Smith, 2018; Grover, Del Greco and König, 2018; Burgess *et al.*, 2020). Primary focus was put on determining

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authors' considerations for the three main assumptions of Mendelian randomisation studies: 1) Instrumental variable is associated with risk factor of interest; 2) There are no confounders between instrumental variable and outcome; 3) Instrumental variable affects outcome only through the risk factor of interest.

Quality assessment questionnaire
1. Are outcome and exposure samples drawn from same ethnic population?
2. Are outcome and exposure samples independent?
3. Assumption 1 - Is there sufficient evidence that the variants are robustly associated with the risk factor?
4. Assumption 2 - Do authors consider confounders of association between genetic variants and outcome?
5. Assumption 3 - Do authors consider other biological mechanism of genetic variants other than risk factor of interest?
6. Are variants manually picked (e.g. to tackle pleiotropy)?
7. Are variants pruned to include independent instruments (linkage disequilibrium)?
8. Are the effect and other alleles coded in the same direction for the exposure and outcome (variable harmonization)?
9. Is MR estimate compared with conventional observational estimate?
10. Is sensitivity analysis performed?
11. Is data available in a supplement or by request to allow researchers to reproduce their findings?

Data extraction

5 Baseline study characteristics will be extracted - title, year of publication, author, exposure(s) and outcome(s).
For the exposure(s) of each study, the following will be extracted:
- Exposure source article title and year
- Cohort
- Cohort inclusion and exclusion criteria
- Covariates
- Sex
- SNP linkage disequilibrium r^2 cut-off
- Number of SNPs

For the outcome(s) of each study, the following will be extracted:
- Outcome source article title and year
- Cohort
- Case sample size
- Control sample size

Data analysis

6 Qualitative data analysis:
Selected data will be summarised with baseline study characteristics as described above, exposure cohort and outcome cohort.

Quantitative data analysis:
Units will be standardised to common units. For studies which presented standard errors, values will be converted to 95% CI. Data will be analysed using the R package 'meta' (Balduzzi, Rücker and Schwarzer, 2019). Odds ratios (OR) from inverse-weighted variance analysis will be pooled to give an overall estimate using fixed effects model for each risk factor. The OR of individual studies, the overall estimates, and 95% CI will be represented on a forest plot.

Heterogeneity analysis:
Assess heterogeneity across studies with I^2 statistics. Increasing value is an indication of heterogeneity where 0-25% is low heterogeneity, 50-75% is moderate heterogeneity, and >75% is high heterogeneity (Higgins *et al.*, 2003). If a study is outside 95% CI, we will perform "one study removed" method to determine if one result is skewing the overall effect size.

Publication bias will be assessed using Funnel plot and Egger's regression.

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Discussion

7 Here we provide a protocol for systematic review and meta-analysis of MR studies investigating risk factors for dementia. Our findings will provide a better insight into the modifiable causes of dementia. This will ultimately contribute with suggestions for interventions and guide future clinical trials. Considering the growing burden of dementia in conjunction with the expansion of primary MR studies, this protocol is timely and may even be adapted for meta-analysis of MR studies investigating other outcomes.

Publication

8 This paper will be submitted as a conference abstract and a journal submission.

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