**Supplementary Material**

**SUPPLEMENTARY METHODS**

**Review Protocol**

**Review question:** Do Mendelian randomization studies suggest causal associations between risk factors and dementia or dementia-related outcomes?

**Population:** Adults (≥18 years)

**Exposure:** Any difference in the level of risk or protective factor indexed by a genetic instrument

**Comparators**: Any comparative measure of the risk factor

**Outcomes:** Cross-sectional and prospective measures of global cognitive function, all-cause dementia and its subtypes (e.g., Alzheimer’s disease, vascular dementia, mixed dementia)

**Search strategy:**

* Searching the following databases: Medline, Embase, PsycINFO (via OvidSP), BIOSIS Citation Index (via Web of Science) and the Cochrane Central Register of Controlled Trials (Central).
* Backward and forward citation searching of included studies

**Search terms relevant to MR**: Mendelian randomization, Mendelian randomisation, instrumental variable

**Search terms relevant to cognition and dementia:** Alzheimer\*, dement\*, cognit\*, neurocogniti\*, neuropsycholog\*, memory

**Study selection criteria:**

**Inclusion criteria:**

* Mendelian randomization studies on the association between risk factors and dementia or dementia-related outcomes
* No language restriction

**Exclusion criteria:**

* Non-genetic studies and genetic studies other than Mendelian randomization
* Studies with outcomes that are not directly dementia-related (e.g., neuroimaging or biomarkers)
* Animal studies
* Case reports, narrative reviews, letters, editorials, opinions
* Conference abstracts
* Duplicate publications using the same data

**Study selection:** Titles and abstracts will be independently screened by two reviewers (EK & IL) using the inclusion/exclusion criteria. Full-texts of potentially relevant studies will be also reviewed independently by the same two reviewers. Any discrepancies will be resolved by discussion with involvement of a third reviewer (EHa or DJL) where necessary.

**Risk of bias assessment:** Risk of bias will be assessed independently by two reviewers (EK & EHa) using the Quality of Genetic Association Studies (Q-Genie) tool [10]. Any discrepancies will be resolved by discussion with involvement of a third reviewer (EHy or DJL) where necessary.

**Data extraction:** Key data including study details, exposures, instrumental variables, population, findings and sources of data will be extracted by one reviewer (EK) and checked by two reviewers (EHa & IL). Any discrepancies will be resolved by discussion with involvement of a third reviewer (EHy or DJL) where necessary.

**Evidence synthesis methods:** We will synthesize narratively genetic evidence on causal associations between risk factors and dementia or dementia-related outcomes.

**Supplementary Fig. 1.** Search strategy in Medline

1 alzheimer\*.tw.

2 cognit\*.tw.

3 memory.tw.

4 Neuropsycholog\*.tw.

5 Dement\*.tw.

6 neurocognit\*.tw.

7 exp Dementia/

8 exp Cognition Disorders/

9 \*Memory Disorders/

10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11 (mendelian adj1 random\*).tw.

12 (instrumental adj1 variable\*).tw.

13 exp Mendelian Randomization Analysis/

14 11 or 12 or 13

15 10 and 14

**Supplementary Fig. 2.** Flowchart of search results and study retrieval

Total identified from electronic database searches: **315**

Full-text articles reviewed for eligibility: **22**

Duplicates: **141**

Excluded after title and abstract screening: **152**

Excluded: **5**

Irrelevant outcome: 2

No Mendelian randomization: 3

Eligible articles: **17**

Identified via backward citation searches and eligible: **1**

Identified via forward citation searches and eligible: **0**

Included in systematic review: **18**

**Supplementary Table 1.** Key characteristics of included studies

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Instrumental variable** | **Exposure** | **Outcome** | **Data source** | **Analytic sample size (casesa)** | **Mean ageb** | **Male, %b** | **Ancestryb** |
| Almeida et al., 2014 [13] | *ADH1B* (rs1229984) | Alcohol consumption | Cognitive impairment (dichotomized at MMSE ≤23) | HIMS (Australia) | 3,542 (502) | 65-83 | 100 | European |
| Au Yeung et al., 2012 [14] | *ALDH2* (rs671) | Alcohol consumption | Global cognition (MMSE) | GBCS (China) | 2,284 | ≥50 | 100 | Asian |
| Au Yeung et al., 2016 [24] | 2 SNPs (rs1008805, rs2175898) | 17β-estradiol | Global cognition (MMSE) | GBCS (China) | 3,066 | ≥50 | 0 | Asian |
| Cruchaga et al., 2012 [7] | *APOE ε2/ε3/ε4* (rs7412, rs429358) | CSF APOE levels | Dementia severity at baseline and 36 months; case-control status for AD at baseline | Knight-ADRC (USA), ADNI (Canada and USA) | 570 (146) | 73.6 | 49.6 | European |
| Hu et al., 2016 [19] | *MTHR* C677T (rs1801133) | Homocysteine | AD | Meta-analysis of 34 case-control studies for AD | 9,397 (4,120) | 73.0c | NR | Mixed |
| Kueider et al., 2016 [20] | 2 SNPs (rs2282679, rs7041) | Vitamin D | Global cognition (MMSE) | BLSA (USA) | 848 | 52.6d | 49.8d | European |
| Kwok et al., 2016 [16] | 3 or 9 SNPs | Coffee consumption | AD | IGAP (international consortia) | 54,162 (17,008) | 74.1e | 41.4e | Europeane |
| Marioni et al., 2011 [8] | *FGB* (rs2227412) | Fibrinogen | General cognitive factor | AAA, ET2DS, LBC1936 (Scotland) | 4,248 | 65.5 | 39.2 | European |
| Mokry et al., 2016[23] | 4 SNPs (rs2282679, rs10741657, rs12785878, rs6013897) | Vitamin D | AD | IGAP (international consortia) | 54,162 (17,008) | 74.1e | 41.4e | Europeane |
| Mukherjee et al., 2015[17] | 29-32 SNPs | BMI | AD (ADGC, GERAD1); dementia probability (HRS) | ADGC (USA), GERAD1 (international consortium), HRS (USA) | AD: 30,146 (13,256); dementia probability: 8,403 | AD: 76.0f; dementia probability: 68.7 | AD: 40.7f; dementia probability: 41.0 | European |
| Nguyen et al., 2016 [11] | 3 SNPs (rs11584700, rs4851266, rs9320913) | Education | Dementia probability | HRS (USA) | 7,981 | ≥50 | 44.2g | European |
| North et al., 2015 [15] | *CHRNA5* (rs16969968 or rs1051730 as a proxy) | Smoking | General fluid intelligence | HALCyon cohorts (UK) | 13,004h | 60.4i | 60.9i | European |
| Østergaard et al., 2015 [12] | 1-73 SNPs | Education, smoking, BMI, total cholesterol, HDL, LDL, SBP, triglycerides, T2D, fasting glucose, insulin resistance | AD | IGAP (international consortia) | 54,162 (17,008) | 74.1e | 41.4e | Europeane |
| Proitsi et al., 2014 [18] | 9-70 SNPs | Total cholesterol, HDL, LDL, triglycerides | AD | MRC-WTCCC2 (UK), GERAD1 (international consortium), MRC Brain cohort (UK), IOP+ (UK), ADNI (Canada and USA) | 10,578 (3,914) | 69.6 | 43.6 | European |
| Quinn et al., 2015 [9] | *F3* (closest gene; D-dimer rs12029080), *FGB* (fibrinogen rs1800789), *SERPINE1* (plasminogen activator inhibitor 1 rs2227631), *VWF* (von Willebrand factor rs1063857) | Blood markers of thrombosis and hemostasis | General cognitive factor | SFHS (Scotland) | 12,757-13,142 | 47.3j | 41.2j | European |
| Walter et al., 2016[21] | 39 SNPs | T2D | AD (IGAP); dementia probability (HRS) | IGAP (international consortium), HRS (USA) | AD: 54,162 (17,008); dementia probability: 8,501 | AD: 71.1e; dementia probability: 68.6 | AD: 41.4e; dementia probability: 42 | Europeane |
| Zhan et al., 2015[25] | 7 SNPs | Telomere length | AD | IGAP (international consortium) | 54,162 (17,008) | 71.1e | 41.4e | Europeane |
| Zhao et al., 2016 [22] | 3 SNPs (rs10046, rs1008805, rs1256031) | Testosterone | Global cognition (MMSE) | GBCS (China) | 4,122 | ≥50 | 100 | Asian |

AAA, Aspirin for Asymptomatic Atherosclerosis trial; AD, Alzheimer’s disease; ADGC, Alzheimer’s Disease Genetics Consortium; ADH1B, alcohol dehydrogenase 1B; ALDH2, aldehyde dehydrogenase 2; ADNI, Alzheimer’s Disease Neuroimaging Initiative; APOE, apolipoprotein E; BLSA, Baltimore Longitudinal Study of Aging; BMI, body mass index; CSF, cerebrospinal fluid; ET2DS, Edinburg type 2 Diabetes Study; FGB, fibrinogen β gene; GBCS, Guangzhou Biobank Cohort Study; GERAD, Genetic and Environmental Risk for Alzheimer’s Disease consortium; GRS, genetic risk score; HALCyon, Healthy Ageing across the Life Course; HDL, high-density lipoprotein cholesterol; HIMS, Health in Men Study; HRS, Health and Retirement Study; IGAP, International Genomics of Alzheimer’s Project; IOP+, Institute of Psychiatry Plus; Knight ADRC, Charles F. and Joanne Knight Alzheimer’s Disease Research Center; LBC1936, Lothian Birth Cohort 1936; LDL, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; MRC-WTCCC2, Medical Research Council Wellcome Trust Case Control Consortium; NR, not reported; SBP, systolic blood pressure; SFHS, Scottish Family Health Study; SNP, single nucleotide polymorphism; T2D, type 2 diabetes; UK, United Kingdom; USA, United States of America;

a Reported for binary outcomes only

b Reported for the analytic sample size unless otherwise stated

c Reported for the sample of 7,600

d Reported for the sample of 1,207 with measured serum 25-hydroxyvitamin D and cognitive function

e Based on previous publication by Lambert and colleagues [27]

f Reported for ADGC sample only (N = 19,692)

g Based on the sample of eligible HRS participants of N = 8,054

h Total number of participants with age, sex, genotype, smoking status and general fluid intelligence factor, and restricted to those included also in the observational analysis

i Reported for participants from five of the HALCyon cohorts included in genetic analyses of the general fluid intelligence factor with age, sex smoking status, socioeconomic position and at least one outcome measure at baseline (N = 15,322)

j Reported for the sample of 18,926

**Supplementary Table 2.** Risk of bias assessment of included studies

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality indicatora** | **Almeida et al. [13]** | **Au Yeung et al. [14]** | **Au Yeung et al. [24]** | **Cruchaga et al. [7]** | **Hu et al. [19]** | **Kueider et al.[20]** | **Kwok et al.[16]** | **Marioni et al. [8]** | **Mokry et al. [23]** | **Mukherjee et al.[17]** | **Nguyen et al.[11]** | **North et al.[15]** | **Østergaard et al.[12]** | **Proitsi et al.[18]** | **Quinn et al. [9]** | **Walter et al.[21]** | **Zhan et al.[25]** | **Zhao et al.[22]** |
| Rationale for study | 5 | 6 | 5 | 3 | 6 | 5 | 5 | 4 | 5 | 6 | 5 | 6 | 4 | 5 | 5 | 5 | 4 | 5 |
| Selection and definition of outcome of interest | 4 | 3 | 3 | 5 | 4 | 5 | 5 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| Selection and comparability of comparison groups | NA | NA | NA | 5 | 4 | NA | 5 | NA | 5 | 5 | NA | NA | 5 | 4 | NA | 5 | 5 | NA |
| Technical classification of the exposure | 6 | 5 | 5 | 5 | 5 | 6 | 4 | 5 | 4 | 5 | 6 | 3 | 4 | 4 | 7 | 4 | 4 | 6 |
| Non-technical classification of the exposure | 5 | 5 | 5 | 3 | 4 | 3 | 4 | 4 | 4 | 3 | 4 | 4 | 4 | 3 | 4 | 4 | 4 | 5 |
| Other sources of bias | 4 | 6 | 4 | 5 | 4 | 5 | 3 | 3 | 5 | 4 | 3 | 5 | 3 | 4 | 3 | 6 | 3 | 5 |
| Sample size and power | 2 | 3 | 3 | 3 | 4 | 1 | 5 | 3 | 6 | 4 | 2 | 4 | 4 | 5 | 4 | 4 | 4 | 3 |
| A priori planning of analyses | 4 | 5 | 5 | 2 | 6 | 6 | 4 | 2 | 6 | 3 | 6 | 4 | 5 | 5 | 2 | 5 | 4 | 6 |
| Statistical methods and control for confounding | 4 | 4 | 5 | 4 | 5 | 5 | 5 | 4 | 5 | 4 | 4 | 4 | 6 | 4 | 4 | 5 | 5 | 4 |
| Testing of assumptions and inferences for MR | 4 | 5 | 4 | 4 | 2 | 6 | 5 | 2 | 5 | 5 | 3 | 4 | 5 | 4 | 3 | 5 | 4 | 5 |
| Appropriateness of inferences drawn from results | 2 | 6 | 5 | 5 | 4 | 5 | 6 | 5 | 6 | 6 | 4 | 4 | 6 | 6 | 6 | 6 | 6 | 6 |
| Total scoreb | 40 | 48 | 44 | 44 | 48 | 47 | 51 | 36 | 56 | 50 | 42 | 43 | 51 | 49 | 43 | 54 | 48 | 49 |
| Overall ratingc | moderate | good | good | moderate | good | good | good | moderate | good | good | good | good | good | good | good | good | good | good |

NA, not applicable; MR, Mendelian randomization.

a Scores range from 1 (poor) to 7 (excellent)

b Higher scores indicate higher overall quality

c Overall rating of poor, moderate or good

**Supplementary Table 3.** Additional results of included studies investigating cardiovascular factors and related biomarkers

|  |  |  |
| --- | --- | --- |
| **Study**  **Exposure (analytic n / casesa)** | **Methods** | **Results**  **MR estimate (95% CI)** |
| Proitsi et al., 2014 [18]  Total cholesterol, HDL, LDL, triglycerides (10,578 / 3,914) | Inverse-variance weighted combination of summary statistics. Results from each cohort were combined with inverse-variance fixed effects meta-analysis | AD  IV estimated OR per total cholesterol GRS unit (full GRS) = 0.965 (0.81, 1.15), p = 0.694  IV estimated OR per HDL GRS unit (full GRS) = 1.003 (0.85, 1.19), p = 0.97  IV estimated OR per LDL GRS unit (full GRS) = 0.947 (0.79, 1.13), p = 0.551  IV estimated OR per triglycerides GRS unit (full GRS) = 1.104 (0.90, 1.36), p = 0.350 |
| Cruchaga et al., 2012 [7]  CSF APOE levels (570 / 146) | GRS is weighted sum of CSF APOE raising alleles;  2SLS regressionb | Dementia severity at baseline  rs2075650 p = 0.006  GRS p = 0.028  Dementia severity at 36 months  rs2075650 p = 0.0013  GRS p = 0.0063  Case-control status at baseline  significant associations per CSF APOE levels |

AD, Alzheimer’s disease; APOE, apolipoprotein E; CI, confidence interval; CSF, cerebrospinal fluid; GRS, genetic risk score; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MR, Mendelian randomization; OR, odds ratio; SNP, single nucleotide polymorphism; 2SLS, two-stage least squares.

a Reported for binary outcomes only

b Adjustment strategy unclear

**Supplementary Table 4.** Additional results of the included study investigating telomere length

|  |  |  |
| --- | --- | --- |
| **Study** | **Methods** | **Results**  **MR estimate (95% CI)** |
| Zhan et al., 2015 [25]  Telomere length (54,162 / 17,008) | Ratio of coefficients | AD  IV estimated OR per SD decrease of telomere length (rs10936599) = 1.16 (0.80, 1.68), p = 0.43  IV estimated OR per SD decrease of telomere length (rs2736100) = 1.93 (1.25, 3.00), p = 0.003  IV estimated OR per SD decrease of telomere length (rs7675998) = 1.13 (0.69, 1.87), p = 0.62  IV estimated OR per SD decrease of telomere length (rs9420907) = 2.13 (1.09, 4.15), p = 0.03  IV estimated OR per SD decrease of telomere length (rs8105767) = 1.06 (0.52, 2.16), p = 0.88  IV estimated OR per SD decrease of telomere length (rs755017) = 0.88 (0.40, 1.96), p = 0.75  IV estimated OR per SD decrease of telomere length (rs11125529) = 1.36 (0.61, 3.03), p = 0.46 |

AD, Alzheimer’s disease; CI, confidence interval; MR, Mendelian randomization; OR, odds ratio