STROBE-MR Checklist of Recommended Items to Address in Reports of Mendelian Randomization Studies

Item No	Section	Checklist item	Addressed?	Response
Introduction				
1	Title and abstract	Indicate mendelian randomization (MR) as the study's design in the title and/or abstract if that is the main purpose of the study	Yes	The title includes the term mendelian randomization and makes it clear that this is the purpose of the study: "Examining the Lancet Commission Risk Factors for Dementia Using Mendelian Randomization" The abstract also makes clear that the purpose of the study is an MR analysis.
2	Background	Explain the scientific background and rationale for the reported study. What is the exposure? Is a potential causal relationship between exposure and outcome plausible? Justify why MR is a helpful method to address the question	Yes	The introduction constructs a logical argument as to why MR is a helpful method and an appropriate tool for this study.
3	Objectives	State specific objectives clearly including prespecified causal hypotheses (if any). State that MR is a method, that under specific assumptions intends to estimate causal effects.	Yes	Objectives of the study are laid out in the last paragraph of the introduction. In the last sentence of the penultimate paragraph of the introduction we state that MR can be used to test causal assumptions given certain assumptions are met.
Methods				
4	Study design and data sources	Present key elements of the study design early in the article. Consider including a table listing sources of data for all phases of the study. For each data source contributing to the analysis, describe the following:	Yes	See Table 1.
	a	Setting: Describe the study design and the underlying population, if possible. Describe the setting, locations and relevant dates, including periods of recruitment, exposure, follow-up and data collection, when available.	Yes	See Table 1 – details of population structure included.
	b	Participants: Report the eligibility criteria and the sources and methods of selection of participants. Report the sample size and whether any power or sample size calculations were carried out prior to the main analysis.	Yes	Max number of participants included in Table 1.
	c	Describe measurement, quality control and selection of genetic variants.		
	d	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases.	Yes	Described in Table 1.
	e	Provide details of ethics committee approval and participant informed consent, if relevant.	NA	All the ethics committee approval and participant consent details are provided in the original studies which have been referenced.
5	Assumptions	Explicitly state the 3-core instrumental variable (IV) assumptions for the main analysis (relevance, independence, and exclusion restriction) as well assumptions for any sensitivity analysis.	Yes	The three assumptions are stated in the introduction section
6	Statistical methods: main analysis	Describe statistical methods and statistics used.	Yes	Included in methods sections
	a	Describe how quantitative variables were handled in the analyses (i.e.	Yes	Included in methods section

		scale, units, model).		
	b	Describe how genetic variants were handled in the analyses and if, applicable, how their weights were selected.	Yes	Included in methods section
	c	Describe the MR estimator (e.g. 2-stage least squares, Wald ratio) and related statistics. Detail the included covariates and, in the case of 2-sample MR, whether the same covariate set was used for adjustment in the 2 samples.	Yes	Included in methods section
	d	Explain how missing data were addressed.	No	Reported in the all the source papers cited in the report.
	e	If applicable, indicate how multiple testing was addressed.	Yes	Included in methods section
7	Assessment of assumptions	Describe any methods or prior knowledge used to assess the assumptions or justify their validity.		
8	Sensitivity analyses and additional analyses	Describe any sensitivity analyses or additional analyses performed (e.g. comparison of effect estimates from different approaches, independent replication, bias analytic techniques, validation of instruments, simulations).	Yes	Included in methods section
9	Software and preregistration			
	a	Name of statistical software and package (s), including version and settings used.	Yes	Included in methods section
	b	State whether the study protocol and details were preregistered (as well as when and where).	NA	Not registered
	Results			
10	Descriptive data			
	a	Report the numbers of individuals at each state of included studies and reasons for exclusion. Consider use of a flow diagram.	Yes	Number of participants reported in Table 1 exact flow of participants can be obtained from the cited papers.
	b	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs proportions).	Yes	Reported in Table 1
	c	If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies.	Yes	Reported in Supplementary materials
	d	For 2-sample MR: i. Provide justification of the similarity of the genetic variant-exposure associations between the exposure and outcome samples. ii. Provide information on the number of individuals who overlap between the exposure and outcome studies.	Yes	Reported in Supplementary materials
11	Main results			
	a	Report the associations between genetic variant and exposure and between genetic variant and outcome, preferably on an interpretable scale.	Yes	Reported in results section and supplementary materials
	b	Report MR estimates of the relationship between exposure and outcome and measures of uncertainty from the MR analysis, on an interpretable scale, such as odds ratio or relative risk per SD difference.	Yes	MR estimates have been transformed to odds ratio with a 95% confidence interval. See results sections.

	c	If relevant consider translating estimates of relative risk into absolute risk for a meaningful time period.	N/A	
	d	Consider plots to visualise results (e.g. forest plot, scatterplot of associations between genetic variants and outcome vs between genetic variants and exposure).	Yes	Forest plots included in results section
12	Assessment of assumptions			
	a	Report the assessment of the validity of the assumptions.		F statistics reported as well as the results from the additional MR tests.
	b	Report any additional statistics (e.g., assessments of heterogeneity across variants, such as I^2, Q statistic or E-value).	Yes	The Q and I^2 are reported in the Supplementary file.
13	Sensitivity analyses and additional analyses			
	a	Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions.	Yes	Sensitivity analysis using MR-Egger and weighted median were conducted. Reported in Supplementary file.
	b	Report results from other sensitivity analyses or additional analyses.	Yes	Additional post-hoc analyses were conducted and reported in the main results section.
	c	Report any assessment of the direction of the causal relationship (e.g. bidirectional MR).	NA	Bidirectionality not assessed in the current study.
	d	When relevant, report and compare with estimates from non-MR analyses.	Yes	The Lancet commission on dementia was referenced.
	e	Consider additional plots visualize results (e.g., leave-one-out analyses).	NA	Not conducted.
	Discussion			
14	Key results	Summarize key results with reference to study objectives.	Yes	First paragraph of discussion.
15	Limitations	Discuss limitations of the study, taking into account the validity of the IV assumptions, other sources of bias, and imprecision. Discuss both direction and magnitude of any potential bias and any efforts to address them.	Yes	Limitations of MR analyses addressed with specific regard to survivor bias.
16	Interpretation			
	a	Meaning: Give a cautions overall interpretation of results in the context of their limitations and in comparison, with other studies.	Yes	See discussion section.
	b	Mechanism: Discuss underlying biological mechanisms that could drive a potential causal relationship between investigated exposure and the outcome, and whether the gene-environment equivalence assumption is reasonable. Use causal language carefully, clarifying that IV estimates may provide causal effects only under certain assumptions.	NA	We did not find robust evidence for causal relationships therefore not applicable.
	c	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions.	Yes	We discuss the value of incorporating the results of MR studies into large reviews of the literature such as the Lancet commission.
17	Generalizability	Discuss the generalizability of the study results (a) to other populations, (b) across other exposure periods/timings, and (c) across other levels of exposure.	NA	Generalizability discussed in the limitations section of the discussion section

	Other Information			
18	Funding	Describe sources of funding and the role of funders in the present study and, if applicable, sources of funding and original study or studies on which the present study is based.	NA	N/A
19	Data and data sharing	Provide the data used to perform all analyses or report where and how the data can be accessed and reference these sources in the article. Provide the statistical code needed to reproduce the results in the article or report whether the code is publicly accessible and, if so, where.	Yes	Code available on GitHub
20	Conflicts of interest	All authors should declare all potential conflicts of interest.	Yes	COI declared