STROBE-MR checklist of recommended items to address in reports of Mendelian randomization studies

Section/item	Item No	Recommendation	Reported on Page Number	Reported on section/Paragraph
Title and abstract	1	Indicate Mendelian randomization (MR) as the study's design in the title and/or the abstract if that is a main purpose of the study	1-2	Title page and Background
Introduction				
Background/ rationale	2	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 study question	4-5	Paragraph1-3
Objectives	3	State specific objectives clearly, including pre-specified causal hypotheses (if any). State that MR is a method that, under specific assumptions, intends to estimate causal effects	5	Paragraph3
Methods				
Study design and Date source	4	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:	Supplementary Table 1	Supplementary Table 1
		a) 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	Supplementary Table 1	Supplementary Table 1
		b) Participants: Give 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	Supplementary Table 1	Supplementary Table 1
		c) Describe measurement, quality control and selection of genetic variants	6	*Selection of instrumental variables*
		d) For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases	NA	
		e) Provide details of ethics committee approval and participant informed consent, if relevant	5-6	*Data source*
Assumptions	5	Explicitly state the three core IV assumptions for the main analysis (relevance, independence and exclusion restriction) as well assumptions for any additional or sensitivity analysis.	5	Paragraph1

Statistial method:main analysis	6	Describe statistical methods and statistics used	6	*Mendelian randomization analysis*
		a) Describe how quantitative variables were handled in the analyses (i.e., scale, units, model)	NA	NA
		b) Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	6	Paragraph3
		c) Describe the MR estimator (e.g. two-stage least squares, Wald ratio) and related statistics. Detail the included covariates and, in case of two-sample MR, whether the same covariate set was used for adjustment in the two samples	NA	NA
		d) Explain how missing data were addressed	NA	NA
		e) If applicable, indicate how multiple testing was addressed	NA	NA
Assessment of assumptions	7	Describe any methods or prior knowledge used to assess the assumptions or justify their validity	6	*Mendelian randomization analysis*
Sensitivity analyses and additional analyses	8	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)	6	*Mendelian randomization analysis*
Software and pre-registration	9	a) Name statistical software and package(s), including version and settings used	6	*Mendelian randomization analysis*
		b) State whether the study protocol and details were pre-registered (as well as when and where)	NA	NA
Results				
Descriptive data	10	a) Report the numbers of individuals at each stage of included studies and reasons for exclusion. Consider use of a flow diagram	NA	NA
		b) Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g.	NA	NA
		c) If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies	NA	NA
		d) For two-sample MR: Provide justification of the similarity of the genetic variant-exposure associations between the exposure and outcome samples. Provide information on the number of individuals who overlap between the exposure and outcome studies	NA	NA

Main results	11	a) Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale	6-7	*Results*
		b) Report MR estimates of the relationship between exposure and outcome, and the measures of uncertainty from the MR analysis, on an interpretable scale, such as odds ratio or relative risk per SD difference	6-7	*Results*
		c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
		d) Consider plots to visualize results (e.g. forest plot, scatterplot of associations between genetic variants and outcome versus between genetic variants and exposure)	Figure 2-6	Figure 2-6
Assessment of assumptions	12	a) Report the assessment of the validity of the assumptions	6-7	*Results*
		b) Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I2, Q statistic or E-value)	Figure 2-6	Figure 3-6
Sensitivity analyses and additional analyses	13	a) Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	6-7	*Results*
		b) Report results from other sensitivity analyses or additional analyses	6-7	*Results*
		c) Report any assessment of direction of causal relationship (e.g., bidirectional MR)	7	Paragraph2
		d) When relevant, report and compare with estimates from non-MR analyses	NA	NA
		e) Consider additional plots to visualize results (e.g., leave-one-out analyses)	NA	NA
Discussion				
Key results	14	Summarize key results with reference to study objectives	7	Paragraph3
Limitations	15	Discuss limitations of the study, taking into account the validity of the IV assumptions, other sources of potential bias, and imprecision. Discuss both direction and magnitude of any potential bias and any efforts to address them	8	Paragraph2

Interpretation	16	a) Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison to other studies	7-10	*Discussion*
		b) Mechanism: Discuss underlying biological mechanisms that could drive a potential causal relationship between the 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	8	Paragraph3-4
			9	Paragraph1-3
		c) Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	10	Paragraph2
Generalizability	17	Discuss the generalizability of the study results (a) to other populations, (b) across other exposure periods/timings, and (c) across other levels of exposure	8	Paragraph2
Other information				
Funding	18	Describe sources of funding and the role of funders in the present study and, if applicable, sources of funding for the databases and original study or studies on which the present study is based	10	*Funding*
Data and data sharing	19	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	Supplementary Table 1	Supplementary Table 1
Conflicts of Interest	20	All authors should declare all potential conflicts of interest	11	*Conflicts of Interest*

The page numbers and relevant texts are to the version of the manuscript at the time of the last submission.

The italics point to the paragraph that corresponds to the subtitle in the manuscript.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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*As the checklist was provided upon initial submission, the page number/line number reported may be changed due to copyediting and may not be referable in the published version. In this case, the section/paragraph may be used as an alternative reference.