

STROBE-MR checklist of recommended items to address in reports of Mendelian randomization studies^{1 2}

Item No.	Section	Checklist item	Page No.	Relevant text from manuscript
1	TITLE and ABSTRACT	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	Title page
INTRODUCTION				
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 study question	4-6	Introduction section
3	Objectives	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	4-6	Introduction section
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:	6-7	Method section, supplementary table
	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.	6-7	Method section GWAS dataset part
	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 the main analysis	6-7	Method section GWAS dataset part
	c)	Describe measurement, quality control and selection of genetic variants	8-10	Method section MR analysis part
	d)	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases	4-6	Introduction section
	e)	Provide details of ethics committee approval and participant informed consent, if relevant	NA	NA
5	Assumptions	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	8-10	Method section MR analysis part
6	Statistical methods: main analysis	Describe statistical methods and statistics used	6-10	Method section

	a)	Describe how quantitative variables were handled in the analyses (i.e., scale, units, model)	6-7	Method section, GWAS dataset part, supplementary table
	b)	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	8-10	Method section
	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	8-10	Method section
	d)	Explain how missing data were addressed	NA	NA
	e)	If applicable, indicate how multiple testing was addressed	6-7	Method section
7	Assessment of assumptions	Describe any methods or prior knowledge used to assess the assumptions or justify their validity	4,8	Introduction and Method section
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)	7-8	Method section
9	Software and pre-registration			
	a)	Name statistical software and package(s), including version and settings used	9	R package section
	b)	State whether the study protocol and details were pre-registered (as well as when and where)	5	Method section

RESULTS

10	Descriptive data			
	a)	Report the numbers of individuals at each stage of included studies and reasons for exclusion. Consider use of a flow diagram	Figure 1	
	b)	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	NA	
	c)	If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies	9-11	Figure 2, Figure 3 and result section
	d)	For two-sample MR: i. Provide justification of the similarity of the genetic variant-exposure associations between the exposure and outcome samples	NA	

	ii. Provide information on the number of individuals who overlap between the exposure and outcome studies	NA	Data from different consortiums	
11	Main results			
	a) Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale	Supplementary table		
	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	Figure 2, Figure 3 and Figure 4		
	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)	NA	Supplementary table	
12	Assessment of assumptions			
	a) Report the assessment of the validity of the assumptions	13-23	Result and discussion section	
	b) Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I^2 , Q statistic or E-value)	13-18	Result section	
13	Sensitivity analyses and additional analyses			
	a) Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	13-18	Result section sensitivity analysis part	
	b) Report results from other sensitivity analyses or additional analyses	17-18	Colocalization and enrichment analysis	
	c) Report any assessment of direction of causal relationship (e.g., bidirectional MR)	13-14	Result section and Figure 1, Figure 2	
	d) When relevant, report and compare with estimates from non-MR analyses	14-15	PLACO with FUMA identified pleiotropic genes	
	e) Consider additional plots to visualize results (e.g., leave-one-out analyses)	NA	Supplementary data	
DISCUSSION				
14	Key results	Summarize key results with reference to study objectives	18	Beginning of discussion section
15	Limitations	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	22-23	Limitation section

16	Interpretation			
	a)	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies	18-22	Discussion section
	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	18-22	Discussion section
	c)	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	18-22	Discussion section
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		
OTHER INFORMATION				
18	Funding	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	26-27	Acknowledgment and funding section
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	26	Data and code availability statement
20	Conflicts of Interest	All authors should declare all potential conflicts of interest	26	Conflict of interest section

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1. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) Statement. JAMA. 2021;under review.
2. Skrivankova VW, Richmond RC, Woolf BAR, Davies NM, Swanson SA, VanderWeele TJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomisation (STROBE-MR): Explanation and Elaboration. BMJ. 2021;375:n2233.