

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	Complete.	
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		In the Introduction (paragraphs 2 and 3), we introduce the exposures of interest and the rationale for using MR to explore the causal question.
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	Complete - Introduction paragraphs 2 and 3.	
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:	Complete - Figure 1 shows the included cohorts and how the analysis populations were selected.	
	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.	Complete - Methods subheading "inclusion criteria and participating cohorts".	
	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	Complete - Figure 1 shows the included cohorts and how the analysis populations were selected.	
	c)	Describe measurement, quality control and selection of genetic variants	Complete - genetic methods are described for each cohort with additional information provided in the supplementary material.	
	d)	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases	Complete - Information provided under subheading "congenital heart disease and other phenotype data".	
	e)	Provide details of ethics committee approval and participant informed consent, if relevant	Complete - relevant information provided in cohort descriptions under "inclusion criteria and participating cohorts".	
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	Complete - Assumptions introduced in the Introduction and then described in relation to the analyses in the "statistical analyses" section of methods.	
6	Statistical methods: main analysis	Describe statistical methods and statistics used		

	a)	Describe how quantitative variables were handled in the analyses (i.e., scale, units, model)	Complete where applicable - Statistical analyses section.
	b)	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	Complete - see "genetic risk score generation" and "statistical analyses".
	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	Complete - see "statistical analyses": we used logistic regression to test for the presence of a causal effect (i.e., we did not use an estimator to try and quantify the causal effect).
	d)	Explain how missing data were addressed	Complete - see Figure 1. We selected on all participants with maternal genotype data and offspring CHD data.
	e)	If applicable, indicate how multiple testing was addressed	NA.
7	Assessment of assumptions	Describe any methods or prior knowledge used to assess the assumptions or justify their validity	Complete - Statistical analyses in relation to the verification of MR assumptions are provided in the statistical analyses 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)	Complete - All analyses and additional analyses are provided in the "statistical analyses" section.
9	Software and pre-registration		
	a)	Name statistical software and package(s), including version and settings used	Complete - See "statistical analyses".
	b)	State whether the study protocol and details were pre-registered (as well as when and where)	Complete - A pre-specified project analysis plan and registration was created on June 3rd 2021: https://doi.org/10.17605/OSF.IO/W62BG

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	Complete - See Figure 1.
	b)	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	Complete - See Table 1.
	c)	If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies	NA.
	d)	For two-sample MR: <ul style="list-style-type: none"> 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	
11	Main results		
		a) Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale	Complete - See Table 2 and Figure 2.
		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	Complete - See Table 2 and Figure 2.
		c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	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)	Complete - See Figure 2.
12	Assessment of assumptions		
		a) Report the assessment of the validity of the assumptions	Complete - See Table 2 and text results.
		b) Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I^2 , Q statistic or E-value)	NA.
13	Sensitivity analyses and additional analyses		
		a) Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	Complete - See results and Supplementary Figures. We performed: analyses additional adjusting for fetal genotype, analyses excluding BiB (due to unique ethnic structure) and multivariable MR analyses,
		b) Report results from other sensitivity analyses or additional analyses	Complete - see comment above.
		c) Report any assessment of direction of causal relationship (e.g., bidirectional MR)	NA.
		d) When relevant, report and compare with estimates from non-MR analyses	NA.
		e) Consider additional plots to visualize results (e.g., leave-one-out analyses)	NA.
DISCUSSION			
14	Key results	Summarize key results with reference to study objectives	Complete - Discussion paragraph 1.
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	Complete - Limitations are discussed throughout the discussion.

16	Interpretation		
	a)	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies	Complete - Done throughout the 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	Possible mechanisms are not discussed in this paper. A key rationale for this work was to try and replicate previous results using negative control analyses where we do touch upon potential mechanisms: https://doi.org/10.1161/JAHA.120.020051 .
	c)	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	Policy relevance is touched upon within the Discussion, but effect sizes are not discussed. As mentioned, we aimed to explore the direction of effects and compare these with previous observational negative control estimates.
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	Complete - See discussion.
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	Funding requirements completed in accordance with journal guidelines.
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	Data and data sharing requirements completed in accordance with journal guidelines.
20	Conflicts of Interest	All authors should declare all potential conflicts of interest	Conflicts of interest statement completed.

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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.