

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

Item No.	Section	Checklist item	Section (paragraph number)
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	Title page & Abstract
	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	Introduction (paragraphs 1-4)
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	Introduction (paragraph 4)
	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:	
	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.	Methods (Data Source for mendelian randomization study) & Table S9
	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	Methods (Data Source for mendelian randomization study) & Table S9
	c)	Describe measurement, quality control and selection of genetic variants	Methods (Data Source for mendelian randomization study & Selection of genetic instruments & Statistical analysis

			of Mendelian randomization paragraph1) & Table S10-Table S20
		d) For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases	Methods (Data Source for mendelian randomization study) & Table S9
		e) Provide details of ethics committee approval and participant informed consent, if relevant	Ethics statement
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	Methods (Selection of genetic instruments & Statistical analysis of Mendelian randomization paragraph 1)
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)	Methods (Data Source for mendelian randomization study)
		b) Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	Methods (Selection of genetic instruments)
		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	Methods (Statistical analysis of Mendelian randomization paragraph 1)
		d) Explain how missing data were addressed	NA
		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	Methods (Selection of genetic instruments & Statistical analysis of Mendelian randomization paragraph 1)
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)	Methods (Statistical analysis of Mendelian randomization paragraph 1)

9	Software and pre-registration	
	a) Name statistical software and package(s), including version and settings used	Methods (Statistical analysis of Mendelian randomization paragraph 2)
	b) State whether the study protocol and details were pre-registered (as well as when and where)	NA

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	Methods (Selection of genetic instruments & Statistical analysis of Mendelian randomization paragraph 1) & Table S10 & Table S12
	b) Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	Methods (Data Source for mendelian randomization study) & Table S9 & Table S21 & Table S22
	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: 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	NA
11	Main results	
	a) Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale	Results (Mendelian randomization analysis for causal association of RC with cancers) & Table S13-Table S20
	b) Report MR estimates of the relationship between exposure and	Results (Mendelian randomization

	outcome, and the measures of uncertainty from the MR analysis, on an interpretable scale, such as odds ratio or relative risk per SD difference	analysis for causal association of RC with cancers) & Table S21-Table S23
	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, scatter plot of associations between genetic variants and outcome versus between genetic variants and exposure)	Figure S4-Figure S9
12	Assessment of assumptions	
	a) Report the assessment of the validity of the assumptions	Results (Mendelian randomization analysis for causal association of RC with cancers) & Table S23 & Table S24 & Figure S4-Figure S7 & Figure S9
	b) Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I^2 , Q statistic or E-value)	Table S21-Table S24
13	Sensitivity analyses and additional analyses	
	a) Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	Results (Mendelian randomization analysis for causal association of RC with cancers) & Table S21-Table S24 & Figure S4-Figure S7 & Figure S9
	b) Report results from other sensitivity analyses or additional analyses	Results (Mendelian randomization analysis for causal association of RC with cancers) & Table S21-Table S24
	c) Report any assessment of direction of causal relationship (e.g., bidirectional MR)	Table S23

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| d) | When relevant, report and compare with estimates from non-MR analyses | Table 3 & Table 4 & Table S2-Table S4 |
| e) | Consider additional plots to visualize results (e.g., leave-one-out analyses) | Figure S4-Figure S7 |

DISCUSSION

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| 14 | Key results | Summarize key results with reference to study objectives | 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 | Discussion (paragraph 5) |
| 16 | Interpretation | <p>a) Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies</p> <p>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</p> <p>c) Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions</p> | <p>Discussion (paragraph 1-5)</p> <p>Discussion (paragraph 2-5)</p> <p>Discussion (paragraph 5)</p> |
| 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 | Discussion (paragraph 5) |

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
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 availability & Table S9
20	Conflicts of Interest	All authors should declare all potential conflicts of interest	Conflicts of Interest

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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.