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	The title and abstract mentioned the related contexts.
	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	2	In "Introduction" section mentioned the related contexts.
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	2-3	The last paragraph in the "Introduction" part.
	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.	4-5	The part of "2.1 Data Sources"
		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	4-5	The part of "2.1 Data Sources"
		c)	Describe measurement, quality control and selection of genetic variants	5-6	The part of "2.2 IVs Selection"
		d)	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases	5-6	The part of "2.2 IVs Selection"
		e)	Provide details of ethics committee approval and participant informed consent, if relevant		
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	5-6	The part of "2.1 Data Source" and "IVs Selection", and Figure 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)	4-6	The part of "2.1 Data Sources" and "2.2 IVs Selection".
		b)	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	4-6	The part of "2.1 Data Sources" and "2.2 IVs Selection".
		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	6	The part of "2.3 MR Analysis" and "2.4 Multivariable MR analysis".
		d)	Explain how missing data were addressed	5	The part of "2.2.1 Identifying exposure-related IVs".
		e)	If applicable, indicate how multiple testing was addressed		
7	**Assessment of assumptions**		Describe any methods or prior knowledge used to assess the assumptions or justify their validity	5-6	The part of "2.1 Data Sources" and "2.2 IVs Selection".
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)	6	The part of "2.5 Sensitivity analysis".
9	**Software and pre-registration**				
		a)	Name statistical software and package(s), including version and settings used	6	"TwoSampleMR" R package in R software
		b)	State whether the study protocol and details were pre-registered (as well as when and where)		
	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	7-8	The part of "3.1 Forward analysis shows differential causal effects of TL on Diabetes and its complications", "3.3 Reverse analysis confirms differential causal effects of diabetes types and complications on TL, with insulin usage as a major influence", Figure 2, Table 1, and Supplementary Materials.
		b)	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	7-8	The part of "3.1 Forward analysis shows differential causal effects of TL on Diabetes and its complications", "3.3 Reverse analysis confirms differential causal effects of diabetes types and complications on TL, with insulin

				usage as a major influence", Figure 2, Table 1, and Supplementary Materials.
		c) If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies	8,11	Multivariate Mendelian randomization analysis adjusted for the use of insulin (ukb-b-15445) to obtain P-values from inverse-variance weighted method (Table 1).
		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	7-8	The part of "3.1 Forward analysis shows differential causal effects of TL on Diabetes and its complications", "3.3 Reverse analysis confirms differential causal effects of diabetes types and complications on TL, with insulin usage as a major influence", Figure 2, Table 1, and 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	7-8	The part of "3.1 Forward analysis shows differential causal effects of TL on Diabetes and its complications", "3.3 Reverse analysis confirms differential causal effects of diabetes types and complications on TL, with insulin usage as a major influence", Figure 2, Table 1, and Supplementary Materials.
		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	7-8	The part of "3.1 Forward analysis shows differential causal effects of TL on Diabetes and its complications", "3.3 Reverse analysis confirms differential causal effects of diabetes types and complications on TL, with insulin usage as a major influence", Figure 2, Table 1, and Supplementary Materials.
		c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
		d) Consider plots to visualize results (e.g. forest plot, scatterplot of associations between genetic variants and outcome versus between genetic variants and exposure)	7-10	Figures 3-4 , and supplementary materials
12	**Assessment of assumptions**			
		a) Report the assessment of the validity of the assumptions	8-10	The part of "3.2 Sensitivity analysis in forward analysis", Figure 3-4, and Supplementary Materials
		b) Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I^2, Q statistic or E-value)	8-10	The part of "3.2 Sensitivity analysis in forward analysis",Figures 3-4, and Supplementary Materials

13	**Sensitivity analyses and additional analyses**				
		a)	Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	8-10	The part of "3.2 Sensitivity analysis in forward analysis",Figures 3-4, and Supplementary Materials
		b)	Report results from other sensitivity analyses or additional analyses	8-10	The part of "3.2 Sensitivity analysis in forward analysis",Figures 3-4, and Supplementary Materials
		c)	Report any assessment of direction of causal relationship (e.g., bidirectional MR)	8-10	The part of "3.2 Sensitivity analysis in forward analysis",Figures 3-4, and Supplementary Materials
		d)	When relevant, report and compare with estimates from non-MR analyses		
		e)	Consider additional plots to visualize results (e.g., leave-one-out analyses)	8-10	The part of "3.2 Sensitivity analysis in forward analysis",Figures 3-4, and Supplementary Materials
	DISCUSSION				
14	**Key results**		Summarize key results with reference to study objectives	12	The first paragraph in the "Discussion" Part
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	14	The last paragraph in the "Discussion" Part
16	**Interpretation**				
		a)	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies	12-13	The first to third paragraphs in the "Discussion" Part
		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	12-14	The second to fourth paragraphs in the "Discussion" Part
		c)	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	14	The fifth paragraph in the "Discussion" Part
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	14-15	The last paragraph in the "Discussion" part, and the part of "Conclusion".
	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	16	The Part of "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	16	The Part of "Availability of data and materials"
20	**Conflicts of Interest**	All authors should declare all potential conflicts of interest	16	The Part of "Competing Interests"

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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.