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	Page 1	Association of Redox Regulatory Drug Target Genes with Psychiatric Disorders
	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	Page 4-5	The brain is a lipid-rich organ, with enormous oxygen consumption, and lack of sufficient antioxidant barriers, which makes brain highly susceptible to oxidative stress imbalance. Back in the last century, the connection between unbalanced oxidative stress and various neuropsychiatric diseases has been found. Additionally, previous clinical trials revealed that some redox regulatory drugs (RRDs), such as N-Acetylcysteine (NAC) and allopurinol, can improve the symptom of psychiatric disorders (i.e., schizophrenia, depression, autism spectrum disorder), which meant that the drug targets of RRD might be the possible targets for psychiatric disorders. Randomized clinical trials (RCTs) are the golden criteria to explore a causal effect of numerous kinds of RRD treatment. However, these approaches are not suitable due the RCTs are expensive and uncertain. Mendelian randomization (MR) study provides a genetic approach which apply the genetic variants associated with an exposure as the instruments to make causal inference on the outcome.
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	Page 5	Aim to identify potential associations between RRD therapy and psychiatric disorders, the two-sample MR analyses were conducted by integrating brain-derived molecular quantitative trait loci (mRNA expression and protein abundance quantitative trait loci [QTL]) and genome-wide association study (GWAS) findings from large-scale psychiatric genetic studies. Cognitive dysfunction is a core symptom in the psychiatric disorders, and some antioxidants have a positive effect on preventing

					the risk of cognitive decline. To uncover the underlying mechanism on the causal effect of antioxidant target on psychiatric disorders, two-step MR analyses were performed by setting antioxidant levels and cognition function as mediators.
	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:	Supplementary material: Table S2	
		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.	NA	
		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	NA	
		c)	Describe measurement, quality control and selection of genetic variants	NA	
		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	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	Page 6	Three crucial assumptions of MR study are listed as follows: 1) a strong association between genetic instrumentals and target proteins, 2) independence of the instruments from confounding factors, and 3) instrumental variables (IVs) influence the psychiatric disorder risk only through the drug targets.
6	**Statistical methods: main analysis**		Describe statistical methods and statistics used	Page 6-11	
		a)	Describe how quantitative variables were handled in the analyses (i.e., scale, units, model)	NA	
		b)	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	Page 7-8	

		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
		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	Page 8-9
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)	Page 9-10
9	**Software and pre-registration**			Page 9-10
		a)	Name statistical software and package(s), including version and settings used	Page 9-10
		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	Page 7-8
		b)	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	Page 7-8; Table S3-S9
		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	Page 12-13; Table S3-S9

		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	Table S3-S9
		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)	Figure 2
12	**Assessment of assumptions**			
		a)	Report the assessment of the validity of the assumptions	Page 12-13
		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	Page 14-15
		b)	Report results from other sensitivity analyses or additional analyses	Page 14-16
		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)	Figure 3
	DISCUSSION			
14	**Key results**		Summarize key results with reference to study objectives	Page 17
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	Page 19-20
16	**Interpretation**			
		a)	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies	NA

		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	Page 17-19
		c)	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	Page 20
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	Page 20
	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	Page 21
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	Page 21
20	**Conflicts of Interest**		All authors should declare all potential conflicts of interest	Page 21

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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.