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	(based on) Mendelian randomization analyses (were performed)
	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	A systematic review and meta-analysis on controversial results suggests that there is an association between anxiety and increased risk of Hypertension based on the evidence from cross-sectional and prospective studies at that moment
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	the aim of this paper was to study causal relationships between blood pressure and anxiety, depressive symptoms, neuroticism and subjective well-being based on GWAS data with the large sample size.
	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	the GWAS datasets on European population for four psychological states, i.e. anxiety, depressive symptoms, neuroticism and subjective well-being were collected respectively
	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	5	Detailed description of subjects' characters can be checked in each study.
	c)	Describe measurement, quality control and selection of genetic variants	5	For each GWAS dataset, all bi-allelic SNPs and imputation score (INFO score) above

					0.9 were considered for next analysis, and ambiguous SNPs were excluded.
		d)	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases	4	All disorders were assessed on the standard diagnostic criteria
		e)	Provide details of ethics committee approval and participant informed consent, if relevant	5	Ethical approval had been obtained in all original studies.
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	MR analysis infers the credible causality of a relation between the exposure and the outcome by leveraging instrumental variables, which are expected to be independent of confounding factors, i.e. associated with that exposure but not with confounding factors associated with outcome
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)	6	explore bidirectional causal links between each psychological state of blood pressure and anxiety, depressive symptoms, neuroticism and subjective well-being and hypertension in frame of Generalized Summary-data-based Mendelian Randomization (GSMR)
		b)	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	6	And r2 = 0.05 as the LD threshold to identify independent SNP based on European population as reference within1000 genome project (phase3)
		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	in frame of Generalized Summary-data-based Mendelian Randomization (GSMR) [19]. This method based on summary-level data utilized independent genome-wide significant SNPs as instrumental variables, i.e. an index of the exposure to test for

				putative causal associations between a risk factor (exposure) and an outcome. Instrumental variants were selected based on the default GWAS threshold of P ≤ 5 × 10−8. And r2 = 0.05 as the LD threshold to identify independent SNP based on European population as reference within1000 genome project (phase3). HEIDI outlier detection was used to filter genetic instruments that played obvious pleiotropic effects on the exposure and outcome. A threshold P value of 0.01 was used for the outlier detection analysis in HEIDI
		d) Explain how missing data were addressed	6	Not applicable
		e) If applicable, indicate how multiple testing was addressed	6	Furthermore, the P values were adjusted with the Bonferroni method by multiplying 32 for multiple test.
7	**Assessment of assumptions**	Describe any methods or prior knowledge used to assess the assumptions or justify their validity	6	genetic variants used as instrumental variables need to meet three assumptions: 1) is associated with the exposure, 2) only affect an outcome via the exposure, 3) and is independent of confounders.
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	A threshold P value of 0.01 was used for the outlier detection analysis in HEIDI
9	**Software and pre-registration**			
		a) Name statistical software and package(s), including version and settings used	6	genetic variants used as instrumental variables need to meet three assumptions: 1) is associated with the exposure, 2) only affect an outcome via the exposure, 3) and is independent of confounders.

		b) State whether the study protocol and details were pre-registered (as well as when and where)	n.a.	Not applicable
	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	The maximum sample size for BP traits for SBP, DBP and PP is 736,650, the minimum one for BP traits is 463, 010 for hypertension. The maximum sample size for psychological states is 463,010 for anxiety, the minimum one is 170,911 for neuroticism.
		b) Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	7	The maximum sample size for BP traits for SBP, DBP and PP is 736,650, the minimum one for BP traits is 463, 010 for hypertension. The maximum sample size for psychological states is 463,010 for anxiety, the minimum one is 170,911 for neuroticism.
		c) If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies	n.a	
		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	There were no subjects overlapping between BP studies and psychological state studies.
11	**Main results**			
		a) Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale	8	1074 independent instrumental SNPs, which are significantly associated with DBP but not with neuroticism
		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	8	With the BP traits as exposure and psychological states as outcome, hypertension and DBP had significant

					causal effects on neuroticism (P= 8.8 E-6 and 0.026, respectively). After adjustment for multiple tests, only DBP is significantly associated with neuroticism (bxy=0.0036, P bonferroni=0.00028, Table 2)
		c)	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a	
		d)	Consider plots to visualize results (e.g. forest plot, scatterplot of associations between genetic variants and outcome versus between genetic variants and exposure)	8	Fig 1
12	**Assessment of assumptions**				
		a)	Report the assessment of the validity of the assumptions	8	These instrumental SNPs with F-statistic >10 are independent with the LD r^2 less than 0.05 and are remained through HEIDI-outlier analysis that can remove horizontal pleiotropic SNPs with P value less than 0.01.
		b)	Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I^2, Q statistic or E-value)	n.a	
13	**Sensitivity analyses and additional analyses**				
		a)	Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	n.a.	
		b)	Report results from other sensitivity analyses or additional analyses	n.a	
		c)	Report any assessment of direction of causal relationship (e.g., bidirectional MR)	8	The reverse causal effects analysis indicated that after clumping and HEIDI-outlier filtering SNPs, less than the default threshold of 10 independent instrumental variants were retained for analyzing the causal effects of each psychological state on BP.

		d)	When relevant, report and compare with estimates from non-MR analyses	n.a	
		e)	Consider additional plots to visualize results (e.g., leave-one-out analyses)	n.a	
	DISCUSSION				
14	**Key results**		Summarize key results with reference to study objectives	9	Here, it is the first time that we utilized GSMR analysis method and found the causal effect of DBP on the neuroticism.
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	9	potential limitations of the current analysis are following
16	**Interpretation**				
		a)	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies	n.a	
		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	9	These intrigue the interests of the role of blood pressure in psychosomatic medicine since the blood pressure is a link factor between brain and heart and may promote the development of personality trait.
		c)	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	9	Persons with neuroticism more frequently experience higher mental stress which in turn can lead to elevated BP and cardiovascular diseases.
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	n.a	
	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	15	Acknowledgement
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	n.a.	

20	**Conflicts of Interest**	All authors should declare all potential conflicts of interest	15	Declaration of competing interest

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.