**S2 checklist: STROBE-MR checklist of recommended items to address in reports of Mendelian randomization studies**

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| Item No. | Section | Checklist item | Where addressed in manuscript |
| 1 | **TITLE andABSTRACT** | Indicate Mendelian randomization (MR) as the study’s design in the title and/or theabstract if that is a main purpose of the study | Title |
|  | **INTRODUCTION** |  |  |
| 2 | **Background** | Explain the scientific background and rationale for the reported study. What is theexposure? Is a potential causal relationship between exposure and outcomeplausible? Justify why MR is a helpful method to address the study question | Introduction – paragraph2 1-3 |
| 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 estimatecausal effects | Introduction – paragraph 4 |
|  | **METHODS** |  |  |
| 4 | **Study design anddata sources** | Present key elements of the study design early in the article. Consider including atable listing sources of data for all phases of the study. For each data sourcecontributing 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. | STable 1 and methods – genetic variants (paragraph 1) |
|  |  | b) Participants: Give the eligibility criteria, and the sources and methods of selection ofparticipants. Report the sample size, and whether any power or sample sizecalculations were carried out prior to the main analysis | STable 1 & methods - genetic variants (paragraph 1) & Mendelian randomization (paragraph 1) |
|  |  | c) Describe measurement, quality control and selection of genetic variants | Methods – genetic variants (paragraph 1) |
|  |  | d) For each exposure, outcome, and other relevant variables, describe methods ofassessment and diagnostic criteria for diseases | Methods – genetic variants (paragraph 1) |
|  |  | e) Provide details of ethics committee approval and participant informed consent, ifrelevant | Methods – genetic variants (paragraph 1) |
| 5 | **Assumptions** | Explicitly state the three core IV assumptions for the main analysis (relevance,independence and exclusion restriction) as well assumptions for any additional orsensitivity analysis | Methods – Mendelian randomization paragraph 1 |
| 6 | **Statistical methods:** | Main analysisDescribe statistical methods and statistics useda) Describe how quantitative variables were handled in the analyses (i.e., scale, units,model) | Not applicable for two-sample MR |
|  |  | b) Describe how genetic variants were handled in the analyses and, if applicable, howtheir weights were selected | Methods – Mendelian randomization paragraph 1 |
|  |  | c) Describe the MR estimator (e.g. two-stage least squares, Wald ratio) and relatedstatistics. Detail the included covariates and, in case of two-sample MR, whether thesame covariate set was used for adjustment in the two samples | Methods – Mendelian randomization paragraph 1 |
|  |  | d) Explain how missing data were addressed | Not applicable for two-sample MR setting here |
|  |  | e) If applicable, indicate how multiple testing was addressed | Methods – Mendelian randomization paragraph 1 |
| 7 | **Assessment ofassumptions** | Describe any methods or prior knowledge used to assess the assumptions or justifytheir validity | Methods – Mendelian randomization paragraph 1 |
| 8 | **Sensitivity analysesand additionalanalyses** | Describe any sensitivity analyses or additional analyses performed (e.g. comparisonof effect estimates from different approaches, independent replication, bias analytictechniques, validation of instruments, simulations) | Methods – Mendelian randomization paragraph 1 |
| 9 | **Software and pre-registration** | a) Name statistical software and package(s), including version and settings used | Methods – Mendelian randomization paragraph 1 |
|  |  | b) State whether the study protocol and details were pre-registered (as well as when andwhere) | Methods – paragraph 1 |
|  | **RESULTS** |  |  |
| 10 | **Descriptive data** | a) Report the numbers of individuals at each stage of included studies and reasons forexclusion. Consider use of a flow diagram | No exclusions, STable 1 for sample sizes |
|  |  | b) Report summary statistics for phenotypic exposure(s), outcome(s), and other relevantvariables (e.g. means, SDs, proportions) | STable 1 for original GWAS papers |
|  |  | c) If the data sources include meta-analyses of previous studies, provide theassessments of heterogeneity across these studies | STable 1 for original GWAS papers |
|  |  | d) For two-sample MR:i. Provide justification of the similarity of the genetic variant-exposure associationsbetween the exposure and outcome samplesii. Provide information on the number of individuals who overlap between theexposure and outcome studies | Methods – genetic variants paragraph 1 |
| 11 | **Main results** | a) Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale | IV-alcohol consumption and IV-iron associations are publically available (STable 1); IV-AUD and IV-QSM associations available upon receipt of successful application |
|  |  | b) Report MR estimates of the relationship between exposure and outcome, and themeasures of uncertainty from the MR analysis, on an interpretable scale, such asodds ratio or relative risk per SD difference | Results – genetic analysis, Fig 4, pathways from alcohol to brain iron (paragraph 3), Fig 6 |
|  |  | c) If relevant, consider translating estimates of relative risk into absolute risk for ameaningful time period | Not applicable |
|  |  | d) Consider plots to visualize results (e.g. forest plot, scatterplot of associations betweengenetic variants and outcome versus between genetic variants and exposure) | Fig 4 & 6 |
| 12 | **Assessment ofassumptions** | a) Report the assessment of the validity of the assumptions | Results – genetic analysis (paragraph 1), pathways from alcohol…(paragraph 3) |
|  |  | b) Report any additional statistics (e.g., assessments of heterogeneity across geneticvariants, such as I 2, Q statistic or E-value) | Results – genetic analysis (paragraph 1) |
| 13 | **Sensitivity analysesand additionalanalyses** | a) Report any sensitivity analyses to assess the robustness of the main results toviolations of the assumptions |  |
|  |  | b) Report results from other sensitivity analyses or additional analyses | SFig 2, SFig 3, SFig 7, SFig 8 |
|  |  | c) Report any assessment of direction of causal relationship (e.g., bidirectional MR) | Not application here  |
|  |  | d) When relevant, report and compare with estimates from non-MR analyses | Results – observational associations paragraph 1  |
|  |  | e) Consider additional plots to visualize results (e.g., leave-one-out analyses) | SFig 2,3,7,8  |
|  | **DISCUSSION** |  |  |
| 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 andmagnitude of any potential bias and any efforts to address them | Discussion, paragraphs 7&8 |
| 16 | **Interpretation** | a) Meaning: Give a cautious overall interpretation of results in the context of theirlimitations and in comparison with other studies | Discussion – paragraphs 2&3 |
|  |  | b) Mechanism: Discuss underlying biological mechanisms that could drive a potentialcausal relationship between the investigated exposure and the outcome, and whetherthe gene-environment equivalence assumption is reasonable. Use causal languagecarefully, clarifying that IV estimates may provide causal effects only under certainassumptions | Discussion – paragraphs 2&3 |
|  |  | c) Clinical relevance: Discuss whether the results have clinical or public policyrelevance, and to what extent they inform effect sizes of possible interventions | Discussion, paragraph 9 |
| 17 | **Generalizability** | Discuss the generalizability of the study results (a) to other populations, (b) acrossother exposure periods/timings, and (c) across other levels of exposure | Discussion, paragraph 8 |
|  | **OTHERINFORMATION** |  |  |
| 18 | **Funding** | Describe sources of funding and the role of funders in the present study and, ifapplicable, sources of funding for the databases and original study or studies onwhich the present study is based | Financial disclosure |
| 19 | **Data and datasharing** | Provide the data used to perform all analyses or report where and how the data canbe accessed, and reference these sources in the article. Provide the statistical codeneeded to reproduce the results in the article, or report whether the code is publiclyaccessible and if so, where | Data availability |
| 20 | **Conflicts ofInterest** | All authors should declare all potential conflicts of interest | Conflicts of interest |