JAMA | Special Communication

Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization
The STROBE-MR Statement

Veronika W. Skrivankova, PhD; Rebecca C. Richmond, PhD; Benjamin A. R. Woolf, MSc; James Yarmolinsky, PhD; Neil M. Davies, PhD; Sonja A. Swanson, ScD; Tyler J. VanderWeele, PhD; Julian P. T. Higgins, PhD; Nicholas J. Timpson, PhD; Niki Dimou, PhD; Claudia Langenberg, PhD; Robert M. Golub, MD; Elizabeth W. Loder, MD; Valentina Gallo, PhD; Anne Tybjaerg-Hansen, MD, DMSc; George Davey Smith, MD, DSc; Matthias Egger, MD; J. Brent Richards, MD

IMPORTANCE Mendelian randomization (MR) studies use genetic variation associated with modifiable exposures to assess their possible causal relationship with outcomes and aim to reduce potential bias from confounding and reverse causation.

OBJECTIVE To develop the STROBE-MR Statement as a stand-alone extension to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline for the reporting of MR studies.

DESIGN, SETTING, AND PARTICIPANTS The development of the STROBE-MR Statement followed the Enhancing the Quality and Transparency of Health Research (EQUATOR) framework guidance and used the STROBE Statement as a starting point to draft a checklist tailored to MR studies. The project was initiated in 2018 by reviewing the literature on the reporting of instrumental variable and MR studies. A group of 17 experts, including MR methodologists, MR study design users, developers of previous reporting guidelines, and journal editors, participated in a workshop in May 2019 to define the scope of the Statement and draft the checklist. The draft checklist was published as a preprint in July 2019 and discussed on the preprint platform, in social media, and at the 4th Mendelian Randomization Conference. The checklist was then revised based on comments, further refined through 2020, and finalized in July 2021.

FINDINGS The STROBE-MR checklist is organized into 6 sections (Title and Abstract, Introduction, Methods, Results, Discussion, and Other Information) and includes 20 main items and 30 subitems. It covers both 1-sample and 2-sample MR studies that assess 1 or multiple exposures and outcomes, and addresses MR studies that follow a genome-wide association study and are reported in the same article. The checklist asks authors to justify why MR is a helpful method to address the study question and state prespecified causal hypotheses. The measurement, quality, and selection of genetic variants must be described and attempts to assess validity of MR-specific assumptions should be well reported. An item on data sharing includes reporting when the data and statistical code required to replicate the analyses can be accessed.

CONCLUSIONS AND RELEVANCE STROBE-MR provides guidelines for reporting MR studies. Improved reporting of these studies could facilitate their evaluation by editors, peer reviewers, researchers, clinicians, and other readers, and enhance the interpretation of their results.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: J. Brent Richards, MD, Jewish General Hospital, 3755 Côte-Ste-Catherine Rd, Ste H-413 Montréal, QC H3T 1E2, Canada (contact@strobe-mr.org).

JAMA. 2021;326(16):1614-1621. doi:10.1001/jama.2021.18236

Mendelian randomization is a method that uses genetic variation associated with modifiable exposures (or risk factors) to assess their possible causal relationship with outcomes, and aims to reduce bias from confounding, including reverse causation, in epidemiological studies.[1-3] Mendelian randomization studies use genetic variants, typically single-nucleotide polymorphisms (SNPs), that are reliably associated with exposures of interest but do not vary with the correlated lifestyle or socioeconomic factors that may confound conventional observational associations. In recent decades, the number of published mendelian randomization studies has increased rapidly, from 1 report in 2003 to more than 800 articles in 2020. Recent studies have addressed topics as diverse as IL-6 receptor inhibition and prognosis of COVID-19,[4] cannabis use and risk of schizophrenia,[5] and association of education and intelligence with risk of Alzheimer disease.[6]

The use of genetic variants for testing hypotheses of causal inference regarding the potential relationship between modifiable exposures and health outcomes depends on the gene-environment equivalence assumption, that modification of the exposure by genetic variation will have the same downstream influence on the outcome as if the exposure were modified through an environmental intervention (including lifestyle and pharmaceutical factors).[7] As noted by Emdin et al,[2] "[m]endelian randomization rests on 3 main assumptions: (1) the genetic variant is associated with the risk factor; (2) the genetic variant is not associated with confounders; and (3) the genetic variant influences the outcome only through the risk factor."

Mendelian randomization can be applied within the instrumental variable framework, if specific assumptions are met. Assumptions are violated if, for example, there is horizontal pleiotropy, in which the genetic variant influences the outcome independently of the risk factor. Also, the variant could be in linkage disequilibrium with another variant that is associated with the outcome or could vary by ancestry.[8,9] Misleading inferences can be generated in mendelian randomization analyses if the relationships relating the exposure to the outcome are misspecified, for example, if the genotype directly affects the outcome, which then affects the putative exposure (ie, reverse causation).

Despite increasing relevance and popularity of mendelian randomization studies, their reporting is often incomplete, which may limit the credibility of potential causal inference.[10-12] Reporting guidelines, such as the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline,[13] can improve reporting quality.[14] STROBE-MR was developed as a guideline for reporting mendelian randomization studies. It is accompanied by an Explanation and Elaboration (E&E) document,[15] which gives the rationale for each item in the checklist and examples of good reporting. This Special Communication describes the development of the STROBE-MR Statement and includes the checklist of recommended items for inclusion in reports of mendelian randomization studies.

Key Points

Question What information should be included in reports of mendelian randomization (MR) studies?

Findings An international expert committee, informed by the methodological framework for guideline development of the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network and using a consensus process, developed the STROBE-MR checklist, which includes 20 main items and 30 subitems for reporting the results of MR studies.

Meaning Use of the STROBE-MR reporting guideline for MR studies could facilitate evaluation by editors, peer reviewers, researchers, clinicians, and other readers, and enhance the interpretation of their results.

STROBE-MR Development Methods

Initial Steps

With increasing evidence that reporting quality of many mendelian randomization studies is inadequate,[10-12] the core group (V.W.S., R.C.R., G.D.S., M.E., J.B.R.) established the STROBE-MR project in 2018. Development of STROBE-MR was informed by the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network's methodological framework for guideline development.[14] First, the literature on the reporting of instrumental variable and mendelian randomization studies was reviewed to identify deficiencies in reporting and previous guidance. Keywords in the article title (*instrumental variable* OR *mendelian randomization*) were combined with *reporting* in the title or abstract. The search was performed in the PubMed database and updated several times during the process of developing the guidance, with the last update on July 8, 2021. Additional literature searches were conducted to identify methodological articles or examples of good reporting.

Second, funding was obtained for the guideline initiative and, specifically, for a face-to-face meeting. A list of potential participants was developed based on the networks of the project's core group and literature searches. Experts in various fields were invited, ranging from mendelian randomization methodologists and authors of previous reporting guidelines to frequent mendelian randomization study design users and scientific journal editors. The list of the 17 meeting participants is available on Open Science Framework (https://osf.io/fpb8g/).[16]

Meeting Preparation

In preparation for the meeting, the core group generated a draft checklist with items that should be reported in mendelian randomization studies. Built on STROBE, the list focused on mendelian randomization–specific assumptions, methods of assessment of their potential violations, and the reporting of data and data sources used in mendelian randomization studies. The draft checklist was tested on a random sample of original articles published in 2018, reporting on mendelian randomization study. PubMed was searched for eligible articles using the MESH term *mendelian randomization analysis* and free text terms *mendelian randomization* and *mendelian randomisation* in the title or abstract.

Of 404 potentially eligible articles (as of April 1, 2019), 20 were randomly selected and scanned to determine whether they contained original research. If not, additional articles were randomly selected until 20 reports of mendelian randomization studies were assessed (of which 10 used a 1-sample and 10 a 2-sample mendelian randomization study design). The sample size of 20 was a pragmatic choice of number of publications that could be reviewed in detail before the meeting in May 2019. The purpose of

Table 1. Glossary of Commonly Used Terms in Mendelian Randomization Studies[a]

Term	Explanation
Mendelian randomization (MR)	A method that uses genetic variation to strengthen possible causal inference regarding modifiable exposures influencing risk of disease or other outcomes. Most MR studies are implemented within an instrumental variable framework, using genetic variants as instrumental variables.
1-Sample MR	A type of MR study in which a single sample of individuals is used to estimate the genetic variant-exposure and genetic variant-outcome associations. This approach requires that the genetic variants, exposures, and outcomes are all measured in the same sample and individual-level data are available on all participants.
2-Sample MR	A type of MR study in which the genetic variant-exposure and genetic variant-outcome associations are estimated in different samples and combined using meta-analysis tools. This approach requires summary-level statistics of the association of each genetic variant in the 2 samples. It does not require individual-level data.
Instrumental variables (IVs)	Variables associated with the exposure of interest, that are not related to confounders, and that affect the outcome only through the exposure.
IV assumptions (core assumptions in MR studies)	Relevance assumption: The genetic variants are associated with the exposure of interest. Independence assumption: The genetic variants share no unmeasured cause with the outcome. Exclusion restriction assumption: The genetic variants do not affect the outcome except through their potential effect on the exposure of interest.
Gene-environment equivalence	The notion that differences in an exposure induced by genetic variation will produce the same downstream effects on health outcomes as differences in the exposure produced by environmental influences.
Genetic variant	A variation in the DNA sequence that is found within a population. Typically, a single-nucleotide polymorphism.
Single-nucleotide polymorphism (SNP)	A genetic variant in which a single base pair in the DNA varies across the population, at an appreciable frequency. SNPs typically have 2 alleles (eg, adenine, cytosine, guanine, or thiamine). If the SNP is associated with the trait, then 1 allele will be associated with a higher value of the trait, the other with a lower value. In MR studies, SNPs are the most common genetic variants used as IVs for a modifiable exposure.
Allele score	A single variable produced by combining information from several SNPs that are associated with a trait or phenotype (eg, blood pressure), which can be used to predict the exposure in an MR study. An allele score is sometimes also referred to as genetic risk score, polygenic score, genetic prediction score, etc.
Linkage disequilibrium	The nonrandom association of alleles at 2 or more loci. This normally occurs within a small region of the genome in the general population. This is a potential source of bias in MR studies.
Horizontal pleiotropy	A situation in which genetic variants affect the outcome via pathways independent of the exposure. This is a violation of the exclusion restriction assumption and a source of bias in MR studies.

[a] Adapted from Davies et al[3] and Wade et al.[20]

this pilot review was to better understand the clarity of items on the first checklist draft and to support the literature on reporting deficiencies. It was not intended to be a systematic review. The draft checklist was sent to meeting participants on May 1, 2019, along with the meeting agenda, the EQUATOR guidance on developing reporting guidelines,[14] the STROBE Statement[13] and E&E document,[17] and other background articles. A formal Delphi process was not performed.

Consensus Meeting

The literature review and pilot study results were presented at a 2-day face-to-face meeting, which took place May 16-17, 2019, at the Medical Research Council Integrative Epidemiology Unit at the University of Bristol. The meeting described the rationale and steps of developing reporting guidelines and included sessions on the empirical evidence on the reporting of instrumental variable and mendelian randomization studies, discussions of the draft checklist, and a session on the publication of STROBE-MR. Selected items were discussed in more detail and a meeting participant was assigned to every item according to expertise and availability. These "item leaders" were tasked with finalizing the wording and covering the item in the E&E document.[15] The agenda of the meeting and other meeting materials are available on Open Science Framework.[16]

Further Consultation and E&E

The draft checklist was published as a preprint in July 2019[18] and debated on the preprint platform, Twitter, and at the 4th Mendelian Randomization Conference.[19] As of July 2021, the preprint had been viewed more than 5000 times and downloaded more than 3500 times.[18] All the comments received at the Mendelian Randomization Conference or obtained from the preprint platform and tweets were subsequently discussed in the core team's video conferences during 2019 and 2020, and implemented in the checklist, as appropriate.

In parallel, the group developed the E&E document. The item leaders wrote a paragraph explaining the rationale for each of their items and provided examples of good reporting for inclusion in the E&E document.[15] A glossary of commonly used terms in mendelian randomization studies was also prepared, drawing on the work of Davies et al[3] and Wade et al.[20] Supplementary educational material was included relating to the key assumptions underlying mendelian randomization studies, their assessment and falsification, and the interpretation of potential causal effect estimates. An abridged version of the STROBE-MR glossary is included in the present article (**Table 1**).

Results

Scope of STROBE-MR

The group agreed that the guidelines should apply to studies that use properties of germline genetic variation to strengthen potential causal inference of modifiable exposures on outcomes. The guidelines are tailored to the majority of such studies that use an instrumental variable framework. They cover both 1-sample and 2-sample mendelian randomization studies that assess or multiple exposures and outcomes and mendelian randomization studies that follow a genome-wide association study and are reported in the same article. For mendelian randomization studies that do not use instrumental variable estimation (eg, some studies of gene-by-environment interaction[21]), some items of the

STROBE-MR checklist will not be applicable. The STROBE-MR guidelines do not apply to genome-wide association studies, which are covered by STREGA[22] (Strengthening the Reporting of Genetic Association Studies), sequencing studies, expression studies, or the traditional observational epidemiology studies covered by STROBE.[13]

Literature Review and Test of Draft Checklist

The literature review identified only a few articles that specifically addressed the reporting of instrumental variable or mendelian randomization studies. Most articles were reviewed before the May 2019 meeting[10-12,23,24] and discussed at the meeting. Two more recent articles published after the meeting were also reviewed.[25,26] Systematic reviews of reporting quality in mendelian randomization studies indicate that many reports of mendelian randomization studies do not clearly state or examine the various assumptions of mendelian randomization methods and report insufficient details on the data sources.[10-12] Testing the draft checklist on the sample of 20 mendelian randomization articles published in 2018 confirmed these deficiencies. For example, none of the 10 2-sample mendelian randomization studies described the underlying exposure and outcome study populations in detail, compared them, or discussed sample overlap. Only 10 studies (50%) reported efforts to test and correct for possible pleiotropy. Details on the imputation of missing genetic data or minor allele frequency cutoffs were missing in 11 of the 20 articles reviewed (55%). Information on the strength of genetic instrument was reported in 10 (50%) of the 20 studies. Ten (50%) of the surveyed publications lacked a discussion of clinical or public health relevance, and 13 (65%) did not address the generalizability of the study results. The pilot testing of the draft checklist informed discussions on revising and refining the STROBE-MR checklist and helped assess clarity of the items. The presentation on the review made at the meeting is available on Open Science Framework.[16]

STROBE-MR Checklist

The STROBE-MR checklist consists of 20 items (**Table 2**) that should be addressed when reporting a mendelian randomization study. Similar to the STROBE checklist,[13] the items are grouped into sections Title and Abstract (item 1), Introduction (items 2-3), Methods (items 4-9), Results (items 10-13), Discussion (items 14-17), and Other Information (items 18-20). Some items contain several subitems related to issues within the same topic. In using the checklist, authors should address all items and subitems, even if some information will have to be reported in the supplementary materials due to space restrictions.

Compared with the original STROBE checklist,[13] which included 22 items and 18 subitems, STROBE-MR has 2 fewer items (20) but 12 more subitems (30). Only 1 subitem (No. 6d) remained unchanged (Table 2). All other items and subitems were modified to address requirements specific to reporting of mendelian randomization studies. Briefly, as suggested by Hernán,[27] in the Introduction the authors should address whether potential causality between exposure and outcome is plausible, justify why mendelian randomization helps to address the question, and describe the causal hypotheses. In the Methods section, investigators should describe the setting, participants, measurement, quality control and selection of genetic variants, and the diagnostic criteria for the outcome of interest for each data source used. Authors should state the 3 core instrumental variable assumptions for the main analysis (relevance, independence, and exclusion restriction; see Table 1), state assumptions for any additional or sensitivity analysis, and provide a detailed description of the statistical methods and statistics used.

In the Results section, authors should summarize the number of individuals at each stage (eg, by using a flow diagram) and the phenotypic exposures and outcomes. The justification for similarity of the genetic variant–exposure associations between the exposure and outcome samples and the overlapping number of individuals in both samples should be reported for 2-sample mendelian randomization studies. Reporting of the main results should include the associations between genetic variant(s) and exposure and between the genetic variant(s) and outcome, as well as the mendelian randomization estimates of the relationship between the exposure and outcome. STROBE-MR gives much emphasis on the transparent reporting of assessments of the validity of the assumptions and sensitivity analyses to assess the robustness of the main results to violations of the assumptions.

In the Discussion section, after summarizing the main results, authors should discuss limitations of the study, focusing on the validity of the instrumental variable assumptions, other sources of potential bias, and imprecision. They should provide a cautious overall interpretation of results and discuss the underlying biological mechanisms that could drive a potential causal relationship between the investigated exposure and the outcome. The clinical or public health policy relevance should be addressed. Under Other Information, authors should provide information to allow others access to the data used and the statistical code needed to replicate the analyses.

Discussion

STROBE-MR was developed to guide authors in reporting mendelian randomization studies, supporting editors and reviewers when considering such studies for publication, and helping readers when critically appraising published articles to decide whether the results are valid and useful. The STROBE checklist was used as the point of departure, thoroughly modifying and adapting it to mendelian randomization studies through an open process in accordance with the guidance for developers of reporting guidelines.[14] The relevant empirical evidence on the reporting of mendelian randomization studies was reviewed, and the first draft of the STROBE-MR checklist was piloted on recently published mendelian randomization studies, with consecutive drafts subjected to an extensive iterative process of consultation. Thus, the checklist presented herein is based on input from a large number of individuals with diverse backgrounds and perspectives. The comprehensive E&E document,[15] which is intended for use alongside the checklist, also benefited greatly from this consultation process.

The publication of the STROBE-MR Statement, together with the E&E document,[15] is a first step toward implementing these reporting guidelines. Next steps include encouraging journals to endorse and support adherence to this guideline, for example, by making materials available on the EQUATOR Network website.[28] Furthermore, this group will collaborate with researchers to

Table 2. STROBE-MR Checklist of Recommended Items to Address in Reports of Mendelian Randomization Studies[a]

Item No.	Section	Checklist item
Title and Abstract		
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.
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.
3	Objectives	State specific objectives clearly, including prespecified causal hypotheses (if any). State that MR is a method that, under specific assumptions, intends to estimate causal effects.
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.
	b	Participants: Report 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.
	c	Describe measurement, quality control, and selection of genetic variants.
	d	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases.
	e	Provide details of ethics committee approval and participant informed consent, if relevant.
5	Assumptions	Explicitly state the 3 core instrumental variable (IV) assumptions for the main analysis (relevance, independence, and exclusion restriction), as well assumptions for any additional or sensitivity analysis.
6	Statistical methods: main analysis	Describe statistical methods and statistics used.
	a	Describe how quantitative variables were handled in the analyses (ie, scale, units, model).
	b	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected.
	c	Describe the MR estimator (eg, 2-stage least squares, Wald ratio) and related statistics. Detail the included covariates and, in case of 2-sample MR, whether the same covariate set was used for adjustment in the 2 samples.
	d	Explain how missing data were addressed.
	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.
8	Sensitivity analyses and additional analyses	Describe any sensitivity analyses or additional analyses performed (eg, comparison of effect estimates from different approaches, independent replication, bias analytic techniques, validation of instruments, simulations).
9	Software and preregistration	
	a	Name statistical software and package(s), including version and settings used.
	b	State whether the study protocol and details were preregistered (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.
	b	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (eg, means, SDs, proportions).
	c	If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies.
	d	For 2-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.
11	Main results	
	a	Report the associations between genetic variant and exposure and between genetic variant and outcome, preferably on an interpretable scale.
	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.
	c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.
	d	Consider plots to visualize results (eg, forest plot, scatterplot of associations between genetic variants and outcome vs between genetic variants and exposure).
12	Assessment of assumptions	
	a	Report the assessment of the validity of the assumptions.
	b	Report any additional statistics (eg, assessments of heterogeneity across genetic variants, such as I^2, Q statistic, or E-value).

(continued)

Table 2. STROBE-MR Checklist of Recommended Items to Address in Reports of Mendelian Randomization Studies[a] (continued)

Item No.	Section	Checklist item
13	Sensitivity analyses and additional analyses	
	a	Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions.
	b	Report results from other sensitivity analyses or additional analyses.
	c	Report any assessment of the direction of the causal relationship (eg, bidirectional MR).
	d	When relevant, report and compare with estimates from non-MR analyses.
	e	Consider additional plots to visualize results (eg, leave-one-out analyses).
Discussion		
14	Key results	Summarize key results with reference to study objectives.
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.
16	Interpretation	
	a	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies.
	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.
	c	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions.
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.
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.
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.
20	Conflicts of interest	All authors should declare all potential conflicts of interest.

[a] Republished with permission from the Equator Network. This checklist is copyrighted by the Equator Network under the Creative Commons Attribution 3.0 Unported (CC BY 3.0) license.

translate the reporting guideline into different languages; the STROBE Statement has been translated from English into Chinese, Spanish, German, Italian, Japanese, Persian, Portuguese, and Greek.[28]

Mendelian randomization is an active and constantly developing field, and these guidelines will therefore likely require periodic updates. Specifically, it is anticipated that increases in data availability, including from novel global sequencing and genome-wide genotyping, within-family designs, and efforts to link health care databases, may require updates to these guidelines. As methods continue to be developed to address new or existing challenges, the guidelines will also be updated accordingly. This group will continue to monitor the literature to help maintain the guidance, particularly the checklist.

The STROBE-MR Statement should not be interpreted as an attempt to prescribe reporting mendelian randomization studies in a rigid format that codifies style, methods, or terminology. The intention is solely to provide guidance on how to report mendelian randomization research clearly and comprehensively. The checklist items should be addressed in sufficient detail and with clarity somewhere in an article, but the order and format for presenting information depend on author preferences and journal style. Moreover, reporting guidelines are not recommendations for designing or conducting studies, although they may contribute to improving methodology.[14] While clarity of reporting is a prerequisite to evaluation, the checklist is not an instrument to evaluate mendelian randomization research quality, and it should not be used for this purpose.[29]

Limitations

This statement has several limitations. First, the statement attempts to provide comprehensive reporting guidelines and describe their generation, but does not describe all methods that can be used to assess all of the assumptions that are required within a mendelian randomization study. Nevertheless, the major assumptions and commonly used methods to assess their validity have been described. Second, as with any consensus document, feedback from the community has been sought and incorporated, and future iterations of this document will be updated to incorporate further feedback from individuals interested in undertaking and interpreting mendelian randomization studies. Thus, the process of properly describing and reporting mendelian randomization studies is an evolving field and will be updated as appropriate. Third, a systematic review has not been undertaken to better understand reporting deficiencies in mendelian randomization studies.

Conclusions

STROBE-MR provides guidelines for reporting mendelian randomization studies. Improved reporting of these studies could facilitate their evaluation by editors, peer reviewers, researchers, clinicians, and other readers, and enhance the interpretation of their results.

ARTICLE INFORMATION

Accepted for Publication: September 24, 2021.

Author Affiliations: Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland (Skrivankova, Egger); Medical Research Council Integrative Epidemiology Unit, University of Bristol, Bristol, United Kingdom (Richmond, Woolf, Yarmolinsky, Davies, Timpson, Davey Smith); Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, United Kingdom (Richmond, Yarmolinsky, Davies, Higgins, Timpson, Davey Smith, Egger); Department of Psychological Science, University of Bristol, Bristol, United Kingdom (Woolf); K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Norway (Davies); Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands (Swanson); Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (VanderWeele); NIHR Bristol Biomedical Research Centre, Bristol, United Kingdom (Higgins, Davey Smith); Nutrition and Metabolism Branch, International Agency for Research on Cancer (IARC/WHO), Lyon, France (Dimou); MRC Epidemiology Unit, University of Cambridge, Cambridge, United Kingdom (Langenberg); Berlin Institute of Health at Charité–Universitätsmedizin Berlin, Berlin, Germany (Langenberg); *JAMA*, Chicago, Illinois (Golub); Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Golub); Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts (Loder); Harvard Medical School, Boston, Massachusetts (Loder); *BMJ*, London, United Kingdom (Loder); Campus Fryslân, University of Groningen, Leeuwarden, the Netherlands (Gallo); Institute of Population Health Sciences, Queen Mary, University of London, London, United Kingdom (Gallo); Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom (Gallo); Section for Molecular Genetics, Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark (Tybjaerg-Hansen); Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa (Egger); Departments of Medicine, Human Genetics, Epidemiology, & Biostatistics, Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, Quebec, Canada (Richards); Department of Twin Research and Genetic Epidemiology, King's College London, University of London, London, United Kingdom (Richards).

Author Contributions: Drs Skrivankova and Egger had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Davey Smith, Egger, and Richards contributed equally to this article.
Concept and design: Skrivankova, Richmond, Yarmolinsky, Swanson, VanderWeele, Timpson, Dimou, Langenberg, Golub, Tybjaerg-Hansen, Davey Smith, Egger, Richards.
Acquisition, analysis, or interpretation of data: Skrivankova, Woolf, Davies, Swanson, Higgins, Dimou, Loder, Gallo, Egger, Richards.
Drafting of the manuscript: Skrivankova, Woolf, Yarmolinsky, VanderWeele, Timpson, Dimou, Langenberg, Davey Smith, Egger, Richards.
Critical revision of the manuscript for important intellectual content: Skrivankova, Richmond, Woolf, Yarmolinsky, Davies, Swanson, VanderWeele, Higgins, Dimou, Langenberg, Golub, Loder, Gallo, Tybjaerg-Hansen, Egger, Richards.
Statistical analysis: Skrivankova.
Obtained funding: Davey Smith, Egger.
Administrative, technical, or material support: Skrivankova, Richmond, Woolf, Yarmolinsky, Davey Smith, Egger, Richards.
Supervision: Davey Smith, Egger, Richards.

Conflict of Interests Disclosures: Dr VanderWeele reported receiving grants from the National Cancer Institute (R01CA222147) during the conduct of the study. Dr Gallo reported reimbursement of travel expenses from the University of Bristol during the conduct of the study. Dr Tybjaerg-Hansen reported consultancies or talks for Akcea, AstraZeneca, Draupnir Bio, Novartis, Sanofi, Silence Therapeutics, and Regeneron. Dr Egger reported receiving grants from the Swiss National Science Foundation (189498) during the conduct of the study. Dr Egger convened the STROBE group and is a member of the CONSORT group. Dr Richards reported receiving personal fees from GlaxoSmithKline and Deerfield Capital and grants from GlaxoSmithKline, Eli Lilly, and Biogen outside the submitted work. No other disclosures were reported.

Funding/Support: The STROBE-MR meeting was funded through a Swiss National Science Foundation personal award (Dr Egger, grant No. 17481). Preparatory work was supported by the same award and by the Medical Research Council Integrative Epidemiology Unit (MC_UU_00011/1), University of Bristol, Bristol, United Kingdom, and the Institute of Social and Preventive Medicine, University of Bern, Switzerland.

Role of Funders/Sponsors: The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: Dr Golub, *JAMA* Deputy Editor, was not involved in the evaluation or review of this manuscript, or in the decision regarding publication. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization. The views expressed in this article are those of the authors and do not necessarily represent those of the Swiss National Science Foundation, National Health Service, the National Institute for Health Research, or the UK Department of Health and Social Care.

Additional Contributions: We are grateful to all the colleagues who commented on previous versions of the STROBE-MR checklist. We are also grateful to the Medical Research Council Integrative Epidemiology Unit within the Bristol Medical School, University of Bristol, United Kingdom, for hosting the May 2019 workshop.

REFERENCES

1. Davey Smith G, Ebrahim S. "Mendelian randomization": can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32(1):1-22. doi:10.1093/ije/dyg070

2. Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. *JAMA*. 2017;318(19):1925-1926. doi:10.1001/jama.2017.17219

3. Davies NM, Holmes MV, Davey Smith G. Reading mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362(362):k601. doi:10.1136/bmj.k601

4. Bovijn J, Lindgren CM, Holmes MV. Genetic variants mimicking therapeutic inhibition of IL-6 receptor signaling and risk of COVID-19. *Lancet Rheumatol*. 2020;2(11):e658-e659. doi:10.1016/S2665-9913(20)30345-3

5. Vaucher J, Keating BJ, Lasserre AM, et al. Cannabis use and risk of schizophrenia: a mendelian randomization study. *Mol Psychiatry*. 2018;23(5):1287-1292. doi:10.1038/mp.2016.252

6. Anderson EL, Howe LD, Wade KH, et al. Education, intelligence and Alzheimer's disease: evidence from a multivariable two-sample mendelian randomization study. *Int J Epidemiol*. 2020;49(4):1163-1172. doi:10.1093/ije/dyz280

7. Davey Smith G. Epigenesis for epidemiologists: does evo-devo have implications for population health research and practice? *Int J Epidemiol*. 2012;41(1):236-247. doi:10.1093/ije/dys016

8. Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol*. 2000;29(4):722-729. doi:10.1093/ije/29.4.722

9. Lawlor DA, Harbord RM, Sterne JAC, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*. 2008;27(8):1133-1163. doi:10.1002/sim.3034

10. Swanson SA, Hernán MA. Commentary: how to report instrumental variable analyses (suggestions welcome). *Epidemiology*. 2013;24(3):370-374. doi:10.1097/EDE.0b013e31828d0590

11. Davies NM, Davey Smith G, Windmeijer F, Martin RM. Issues in the reporting and conduct of instrumental variable studies: a systematic review. *Epidemiology*. 2013;24(3):363-369. doi:10.1097/EDE.0b013e31828abafb

12. Boef AGC, Dekkers OM, le Cessie S. Mendelian randomization studies: a review of the approaches used and the quality of reporting. *Int J Epidemiol*. 2015;44(2):496-511. doi:10.1093/ije/dyv071

13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806-808. doi:10.1136/bmj.39335.541782.AD

14. Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Med*. 2010;7(2):e1000217. doi:10.1371/journal.pmed.1000217

15. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian

Randomisation (STROBE-MR): explanation and elaboration. *BMJ*. 2021;375:n2233.

16. Egger M; STROBE-MR Guideline Development Group. Materials for face-to-face meeting of STROBE-MR guideline development group, Bristol, 2019. Accessed January 24, 2021. https://osf.io/fpb8g/

17. Vandenbroucke JP, von Elm E, Altman DG, et al; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med*. 2007;4(10):e297. doi:10.1371/journal.pmed.0040297

18. Davey Smith G, Davies NM, Dimou N, et al. STROBE-MR: guidelines for strengthening the reporting of mendelian randomization studies. Published July 15, 2019. Accessed September 28, 2021. doi:10.7287/peerj.preprints.27857v1

19. MRC Integrative Epidemiology Unit, University of Bristol. 4th Mendelian Randomization Conference 2019. Accessed July 10, 2019. https://www.bristol.ac.uk/integrative-epidemiology/seminars/2019/mr-conference-2019.html

20. Wade K, Lawlor D, Borges MC, et al. MR Dictionary: about. Accessed June 20, 2021. https://mr-dictionary.mrcieu.ac.uk/about/

21. Davey Smith G. Mendelian randomization for strengthening causal inference in observational studies: application to gene × environment interactions. *Perspect Psychol Sci*. 2010;5(5):527-545. doi:10.1177/1745691610383505

22. Little J, Higgins JPT, Ioannidis JPA, et al; STrengthening the REporting of Genetic Association Studies. Strengthening the Reporting of Genetic Association Studies (STREGA): an extension of the STROBE statement. *PLoS Med*. 2009;6(2):e22. doi:10.1371/journal.pmed.1000022

23. MacKenzie TA, O'Malley AJ, Bekelis K. Reporting of baseline characteristics to accompany analysis by instrumental variables. *Epidemiology*. 2018;29(6):817-820. doi:10.1097/EDE.0000000000000914

24. Boef AGC, Dekkers OM, le Cessie S, Vandenbroucke JP. Reporting instrumental variable analyses. *Epidemiology*. 2013;24(6):937-938. doi:10.1097/01.ede.0000434433.14388.a1

25. Lor GCY, Risch HA, Fung WT, et al. Reporting and guidelines for mendelian randomization analysis: a systematic review of oncological studies. *Cancer Epidemiol*. 2019;62:101577. doi:10.1016/j.canep.2019.101577

26. Diemer EW, Labrecque JA, Neumann A, Tiemeier H, Swanson SA. Mendelian randomisation approaches to the study of prenatal exposures: a systematic review. *Paediatr Perinat Epidemiol*. 2021;35(1):130-142. doi:10.1111/ppe.12691

27. Hernán MA. The C-word: scientific euphemisms do not improve causal inference from observational data. *Am J Public Health*. 2018;108(5):616-619. doi:10.2105/AJPH.2018.304337

28. EQUATOR Network. Enhancing the Quality and Transparency of Health Research. Accessed April 10, 2019. https://www.equator-network.org/

29. da Costa BRR, Cevallos M, Altman DGDG, et al. Uses and misuses of the STROBE statement: bibliographic study. *BMJ Open*. 2011;1(1):e000048. doi:10.1136/bmjopen-2010-000048