A New Tool for Reporting Mediation Analyses

To the Editor:

The use of methods for causal mediation analysis has expanded dramatically in epidemiology over the past decade. Epidemiologic journals have themselves been the source of many of the methodologic developments. With the use of mediation methods steadily increasing in epidemiology, there is need also to reflect upon reporting practices when these methods are employed in empirical studies. These considerations in part motivated the development of AGReMA, a Guideline for Reporting Mediation Analyses of randomized trials and observational studies.[1]

AGReMA is an evidence- and consensus-based reporting guideline that provides consolidated recommendations for reporting mediation analyses. Through this set of recommendations,[1] the AGReMA initiative aims to improve the completeness, consistency, and accuracy in reporting mediation analyses. The scope of AGReMA covers primary and secondary mediation analyses of randomized trials and observational studies, and it is intended to be general. The guidelines encourage authors to use the 25-item AGReMA Statement for studies in which mediation analysis is the primary focus, and a 9-item short form, AGReMA-SF, for studies in which mediation analysis is a secondary focus, for example when mediation analyses are supplementary to the main randomized trial or observational study.

The AGReMA statement was developed using the Enhancing Quality and Transparency of Health Research (EQUATOR) methodologic framework for developing reporting guidelines.[2] This included an overview of systematic reviews to assess the need for a guideline[3]; systematic reviews of relevant evidence on reporting practices[4]; a Delphi study[5] that rated the importance of proposed reporting items by panel members (methodologists, statisticians, clinical trialists, epidemiologists, psychologists, applied clinical researchers, clinicians, implementation scientists, evidence synthesis experts, representatives from the EQUATOR Network, and journal editors); an international consensus meeting; and a 4-week external review and pilot test among potential users of AGReMA. Full details on the process of the development of AGReMA are given elsewhere.[1] The resulting AGReMA checklists can be found in the Table and at https://agrema-statement.org; the AGReMA short form consists of items 4, 9, 11, 12, 14, 17, 18, 20, and 21 of the full checklist.

Consistent with Epidemiology's editorial policies concerning guidelines,[6] the present authors are not proposing AGReMA as a standard to be imposed on all papers conducting mediation analyses. Rather AGReMA is being put forward as a tool to help applied researchers reflect upon what can and should be reported. Each study is distinct and comes with its own set of challenges, and varying degrees of attention should be devoted to the various reporting elements as the circumstances and particularities of each study demand. Indeed, the two-tiered (25-item versus 9-item) checklists for mediation analyses, that are either primary or secondary with respect to a given paper, is itself an acknowledgment that different circumstances will merit different levels of detail of reporting. Again, AGReMA is not intended as a proposed universal requirement, but rather as a helpful tool to reflect upon reporting practices for mediation analyses.

Reflection upon reporting practices itself also has the potential to improve the conduct and understanding of mediation analyses. For example, it is still the case that the vast majority of papers reporting mediation analyses do not discuss the assumptions (e.g., control for mediator-outcome confounders) that underlie such analyses.[4] By proceeding through a reporting checklist, investigators may thus encounter, and come to reflect upon, assumptions, challenges, and issues of interpretation, which might otherwise not be given adequate attention. In this way, a reporting checklist can also help to both improve the conduct of mediation analysis and further serve as an educational tool. Many of the readers of the journal Epidemiology are themselves methodologists and this new reporting guideline may prove to be a useful tool to pass along to less methodologically oriented epidemiologists and clinical researchers to encourage greater reflection on the assumptions, implementation, interpretation, as well as reporting of mediation analyses. While courses, tutorials, and textbooks[7] are undoubtedly essential in educational efforts concerning methodology, often learning takes place through practice and implementation, and in this regard, a reporting guideline can be helpful as well. AGReMA is thus not being put forward as a guideline to which all authors and journals are to conform, but rather as a helpful tool for education, for improving implementation, and, of course, for enabling better reporting.

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TABLE. AGReMA Checklist, a Guideline for Reporting Mediation Analyses of Randomized Trials and Observational Studies

Section/Topic	Item Number	Item Description	Reported on Page No.
Title and abstract			
Title	1	Identify that the study uses mediation analysis	
Abstract	2	Provide a structured summary of the objectives, methods, results, and conclusions specific to mediation analyses	
Introduction			
Background and rationale	3	Describe the study background and theoretical rationale for investigating the mechanisms of interest. Include supporting evidence or theoretical rationale for why the intervention or exposure might have a causal relationship with the proposed mediators. Include supporting evidence or theoretical rationale for why the mediators might have a causal relationship with the outcomes	
Objectives	4	State the objectives of the study specific to the mechanisms of interest. The objectives should specify whether the study aims to test or estimate the mechanistic effects	
Methods			
Study registration	5	If applicable, provide references to any protocols or study registrations specific to the mediation analysis, and highlight any deviations from the planned protocol	
Study design and source of data	6	Specify the design of the original study that was used in mediation analyses and where the details can be accessed, supported by a reference. If applicable, describe study design features that are relevant to mediation analyses	
Participants	7	Describe the target population, eligibility criteria specific to mediation analyses, study locations, and study dates (start of participant enrollment and end of follow-up)	
Sample size	8	State whether a sample size calculation was conducted for mediation analyses. If so, explain how it was calculated	
Effects of interest	9	Specify the effects of interest	
Assumed causal model	10	Include a graphic representation of the assumed causal model including the exposure, mediator, outcome, and possible confounders	
Causal assumptions	11	Specify assumptions about the causal model	
Measurement	12	Clearly describe the interventions or exposures, mediators, outcomes, confounders, and moderators that were used in the analyses. Specify how and when they were measured, the measurement properties, and whether blinded assessment was used	
Measurement levels	13	If relevant, describe the levels at which the exposure, mediator, and outcome were measured	
Statistical methods	14	Describe the statistical methods used to estimate the causal relationships of interest. This description should specify analytical strategies used to reduce confounding, model building procedures, justification for the inclusion or exclusion of possible interaction terms, modeling assumptions, and methods used to handle missing data. Provide a reference to the statistical software and package used	
Sensitivity analyses	15	Describe any sensitivity analyses that were used to explore causal or statistical assumptions and the influence of missing data	
Ethical approval	16	Name the institutional research board or ethics committee that approved the study. Provide a description of participant informed consent or ethics committee waiver of informed consent	
Results			
Participants	17	Describe baseline characteristics of participants included in mediation analyses. Report the total sample size and number of participants lost during follow-up or with missing data	
Outcomes and estimates	18	Report point estimates and uncertainty estimates for the exposure-mediator and mediator-outcome relationships. If inference concerning the causal relationship of interest is considered feasible given the causal assumptions, report the point estimate and uncertainty estimate	
Sensitivity parameters	19	Report the results from any sensitivity analyses used to assess robustness of the causal or statistical assumptions, and the influence of missing data	
Discussion			
Limitations	20	Discuss the limitations of the study including potential sources of bias	
Interpretation	21	Interpret the estimated effects considering the study's magnitude and uncertainty, plausibility of the causal assumptions, limitations, generalizability of the findings, and results from relevant studies	
Implications	22	Discuss the implications of the overall results for clinical practice, policy, and science	
Other information			
Funding and role of sponsor	23	List all sources of funding or sponsorship for the mediation analysis and the role of the funders/sponsors in the conduct of the study, writing of the manuscript, and decision to submit for publication.	
Conflicts of interest and financial disclosures	24	State any conflicts of interest and financial disclosures for all authors	
Data and code	25	Authors are encouraged to provide a statement for sharing data and code for the mediation analysis	

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REFERENCES

1. Lee H, Cashin AG, Lamb SE, et al; AGReMA group. A guideline for reporting mediation analyses of randomized trials and observational studies: the AGReMA Statement. *JAMA.* 2021;326:1045–1056.
2. Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Med.* 2010;7:e1000217.
3. Cashin AG, Lee H, Lamb SE, et al. An overview of systematic reviews found suboptimal reporting and methodological limitations of mediation studies investigating causal mechanisms. *J Clin Epidemiol.* 2019;111:60–68.e1.
4. Vo TT, Superchi C, Boutron I, Vansteelandt S. The conduct and reporting of mediation analysis in recently published randomized controlled trials: results from a methodological systematic review. *J Clin Epidemiol.* 2020;117:78–88.
5. Cashin AG, McAuley JH, Lamb S, et al. Items for consideration in a reporting guideline for mediation analyses: a Delphi study. *BMJ Evid Based Med.* 2021;26:106.
6. Lash TL. Getting over TOP. *Epidemiology.* 2022;33:1–6.
7. VanderWeele TJ. *Explanation in Causal Inference: Methods for Mediation and Interaction*. Oxford University Press; 2015.

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