Clinical Review & Education

JAMA | Special Communication

A Guideline for Reporting Mediation Analyses of Randomized Trials and Observational Studies
The AGReMA Statement

Hopin Lee, PhD; Aidan G. Cashin, PhD; Sarah E. Lamb, DPhil; Sally Hopewell, DPhil; Stijn Vansteelandt, PhD; Tyler J. VanderWeele, PhD; David P. MacKinnon, PhD; Gemma Mansell, PhD; Gary S. Collins, PhD; Robert M. Golub, MD; James H. McAuley, PhD; and the AGReMA group

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Lee, H., Cashin, A. G., Lamb, S. E., Hopewell, S., Vansteelandt, S., VanderWeele, T. J., ... & Henschke, N. (2021). A Guideline for Reporting Mediation Analyses of Randomized Trials and Observational Studies: The AGReMA Statement. *JAMA*, *326*(11), 1045-1056.

Agenda

- Overview of Mediation analysis
- Reporting Guidelines for RCTs and Observational studies
- A Guideline for Reporting Mediation Analyses of Randomized Trials and Observational Studies: The AGReMA Statement

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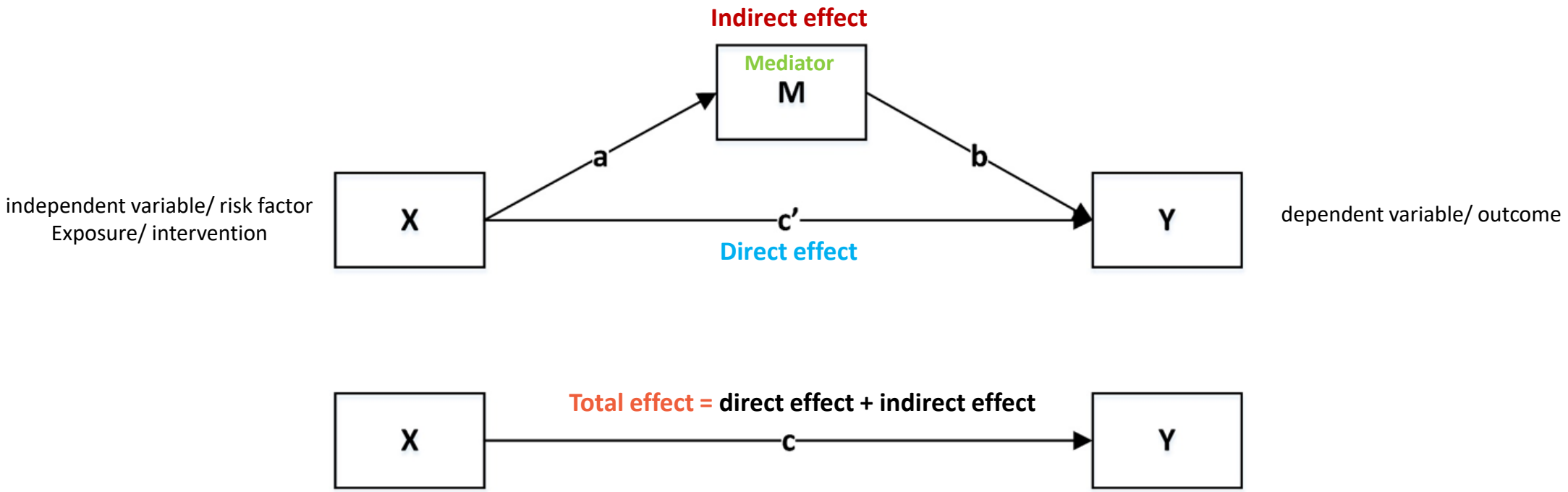
MEDIATION ANALYSIS (MA)

A method to explore …

"The causal pathway from **X** (independent variable/exposure/risk factor) to **Y** (dependent variable/outcome) through **M** (others) to understand underlying pathways of the effects of X on Y."

- The direct effect of X on Y can be observed as well as
- the indirect effect of X on Y that is mediated through other variables, which are called **"mediators" (M) or intermediate variable.**

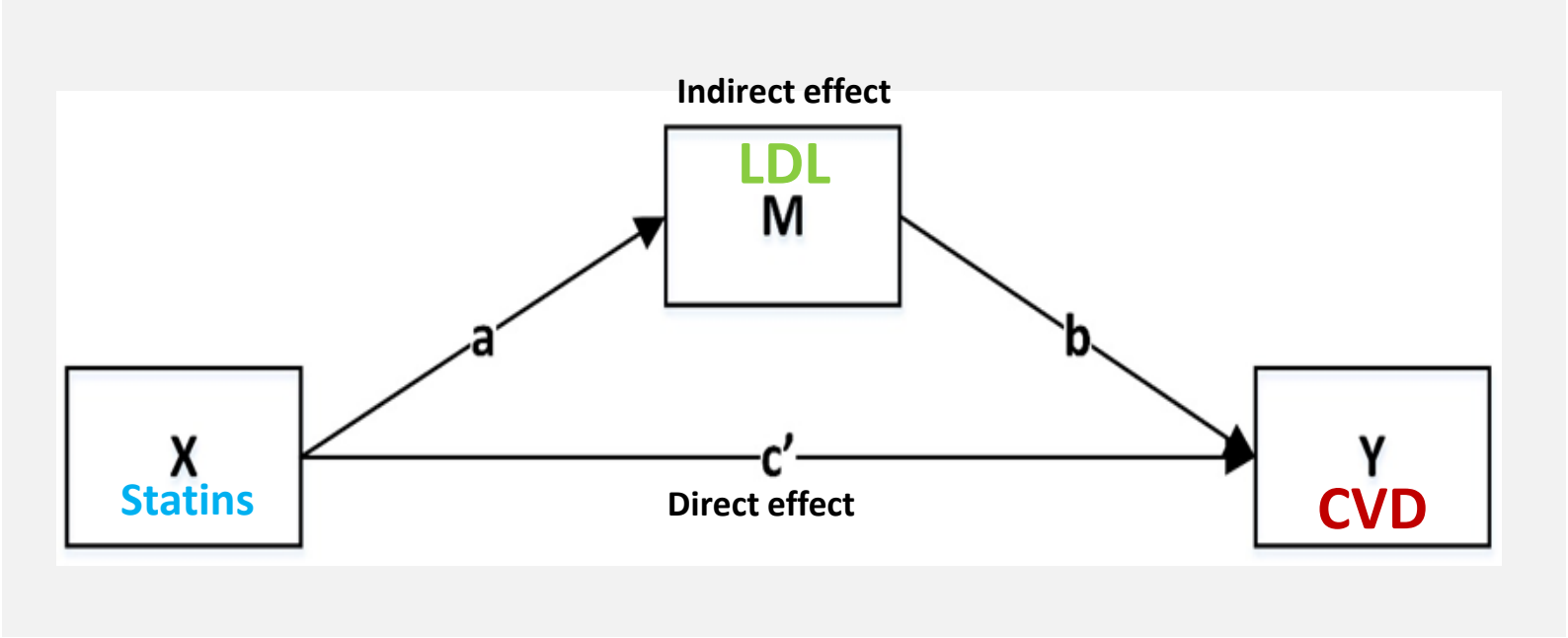


MEDIATION ANALYSIS (MA)

MA is focusing on mechanism evaluation.

- High LDL is an important risk factor of CVD.
- Statins reduced blood LDL.
- Statins are also know to be anti-inflammatory effects.
- Statins reduced CVD risk
- How do we know the reduction of CVD risk is a result of lowering LDL?

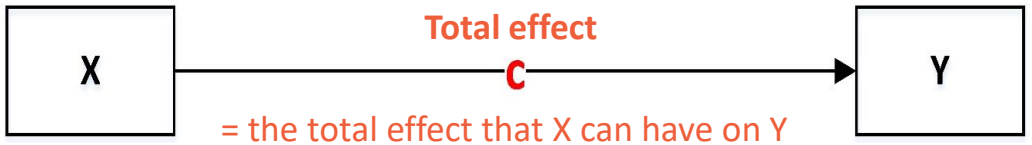
Example

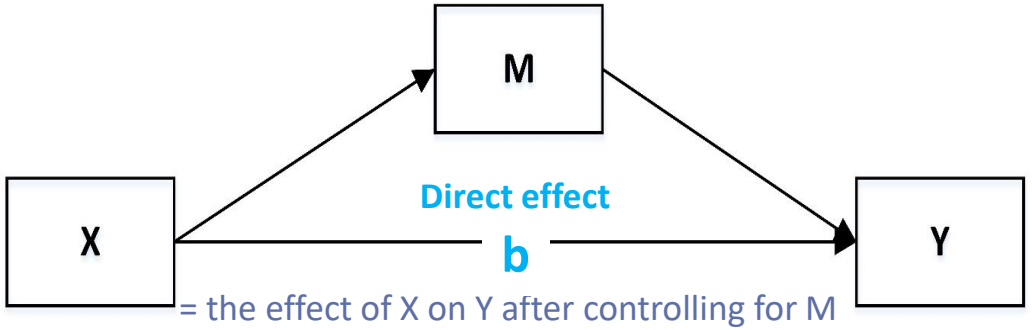


MEDIATION ANALYSIS (MA)

- **Single mediation analysis:** only 1 mediator
  - Traditional approach:

1) **Different method (Difference-of-coefficient approach)**





= the mediated effect is estimated by comparing the relations between the independent variable X and the dependent variable Y from Equations 1 and 2, where the effect of X on Y is estimated with and without adjusting for the mediator M.

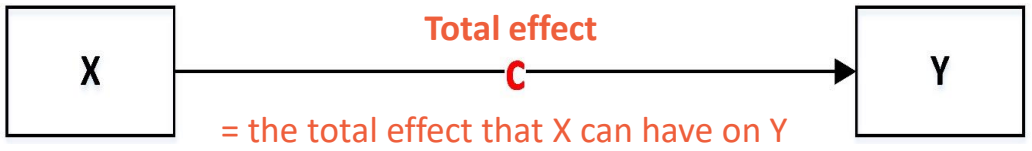
- $E(Y|X, C) = c_0 + cX + c_1C$ …(1)
- $E(Y|X, M, C) = b_0 + bX + b_1M + b_2C$ …(2)

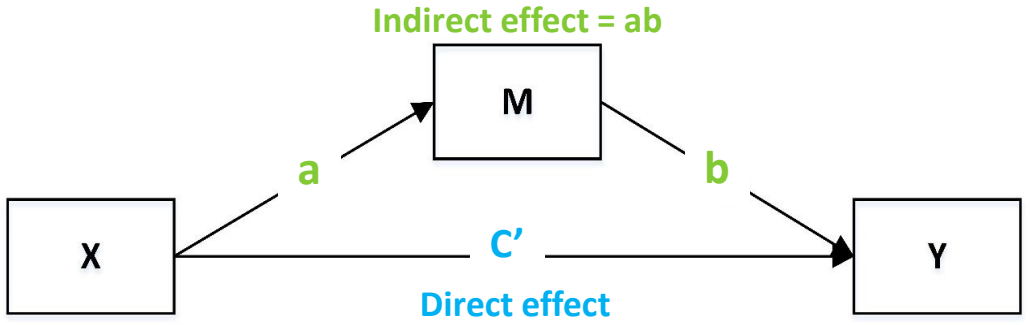
- H_0: **c** = **b**
- H_a: **c** ≠ **b**

MEDIATION ANALYSIS (MA)

- **Single mediation analysis:** only 1 mediator
  - Traditional approach:

    2) **Product method (Product-of-coefficient approach)**





= the mediated effect is estimated by the product of a and b (= ab), from mediator and outcome model.

- Mediator model
  - $E(M|X, C) = a_0 + aX + a_1C$
- Outcome model
  - $E(Y|X, M, C) = b_0 + C'X + bM + b_2C$

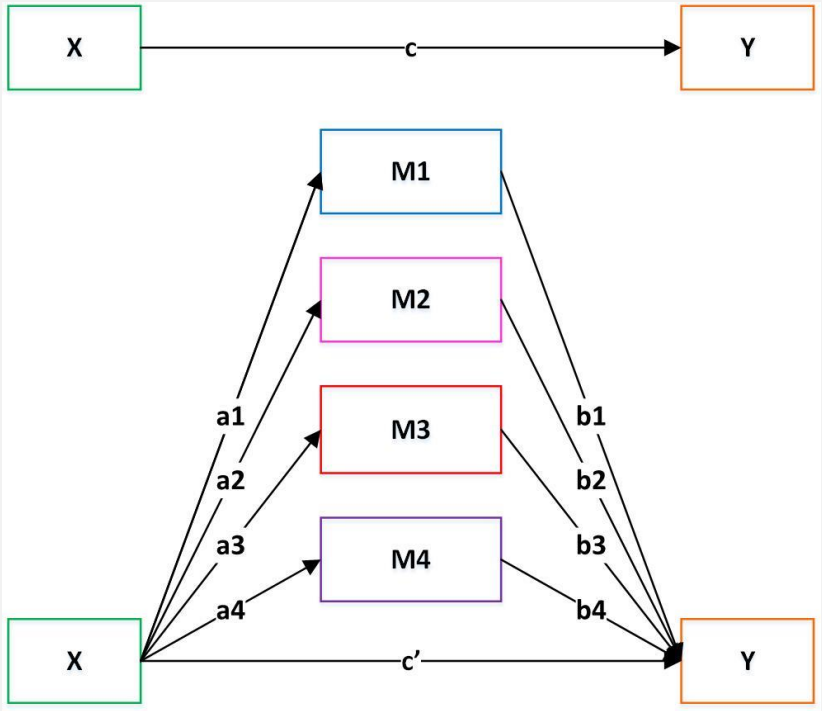
Direct effect (DE) = C'
Indirect effect (IE) = ab
Total effect (C) = C' + ab

- H_0: ab = 0 (The sum of indirect effects would be zero = no mediated effect)
- H_a: ab ≠ 0

MEDIATION ANALYSIS (MA)

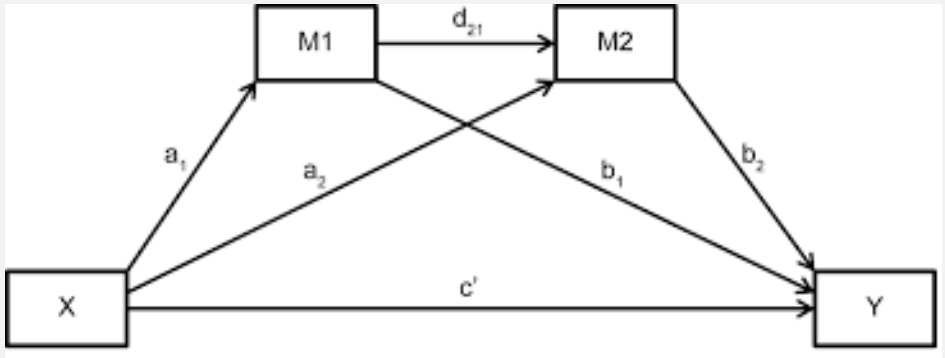
- **Multiple mediation analysis :** > 1 mediator

1. Parallel multiple mediator model (PMMM)



Total IE = a_1b_1 + a_2b_2 +a_3b_3 + a_4b_4

2. Serial multiple mediator model (SMMM)



Total IE = summation of product of coefficients from all possible pathways that pass through mediators

= $a_1b_1 + a_1d_{21}b_2 + a_2b_2$

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INTRODUCTION

- The use of MA has become increasingly common in recent years.
- Researchers have used MA to understand the causal mechanisms by which exposures and interventions exert their effects on health outcomes.
- Commonly, MA is applied to *both RCTs and observational studies* and sometimes reported separate to the original study.
- However, the reporting of studies that use mediation analysis to investigate causal mechanisms of healthcare interventions is varied and often incomplete.

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REPORTING GUIDELINE OF RCTS AND OBSERVATIONAL STUDIES

equator network

Enhancing the QUAlity and Transparency Of health Research

Reporting guidelines for main study types

Randomised trials	CONSORT	Extensions
Observational studies	STROBE	Extensions
Systematic reviews	PRISMA	Extensions
Study protocols	SPIRIT	PRISMA-P
Diagnostic/prognostic studies	STARD	TRIPOD
Case reports	CARE	Extensions
Clinical practice guidelines	AGREE	RIGHT
Qualitative research	SRQR	COREQ
Animal pre-clinical studies	ARRIVE	
Quality improvement studies	SQUIRE	Extensions
Economic evaluations	CHEERS	

Existing reporting guidelines such as

- the CONSORT for RCTs
- STROBE for observational studies.
- their extensions

are not directly applicable to MA, and there is no specific guidance for the reporting of studies that use mediation analysis.

https://www.equator-network.org/

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Clinical practice guidelines	AGREE	RIGHT
Qualitative research	SRQR	COREQ
Animal pre-clinical studies	ARRIVE	
Quality improvement studies	SQUIRE	Extensions
Economic evaluations	CHEERS	

- Specific reporting guideline for MA is required.
- It would guide researchers to transparently report a minimum set of items that would represent the methodology and findings, in particular, reflecting issues that may introduce or prevent bias.

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OBJECTIVE

- to develop an evidence- and consensus-based reporting guideline for studies reporting.

  (A Guideline for Reporting Mediation Analyses; AGReMA)

- to produce a long and short form to support primary or secondary reports of MA.

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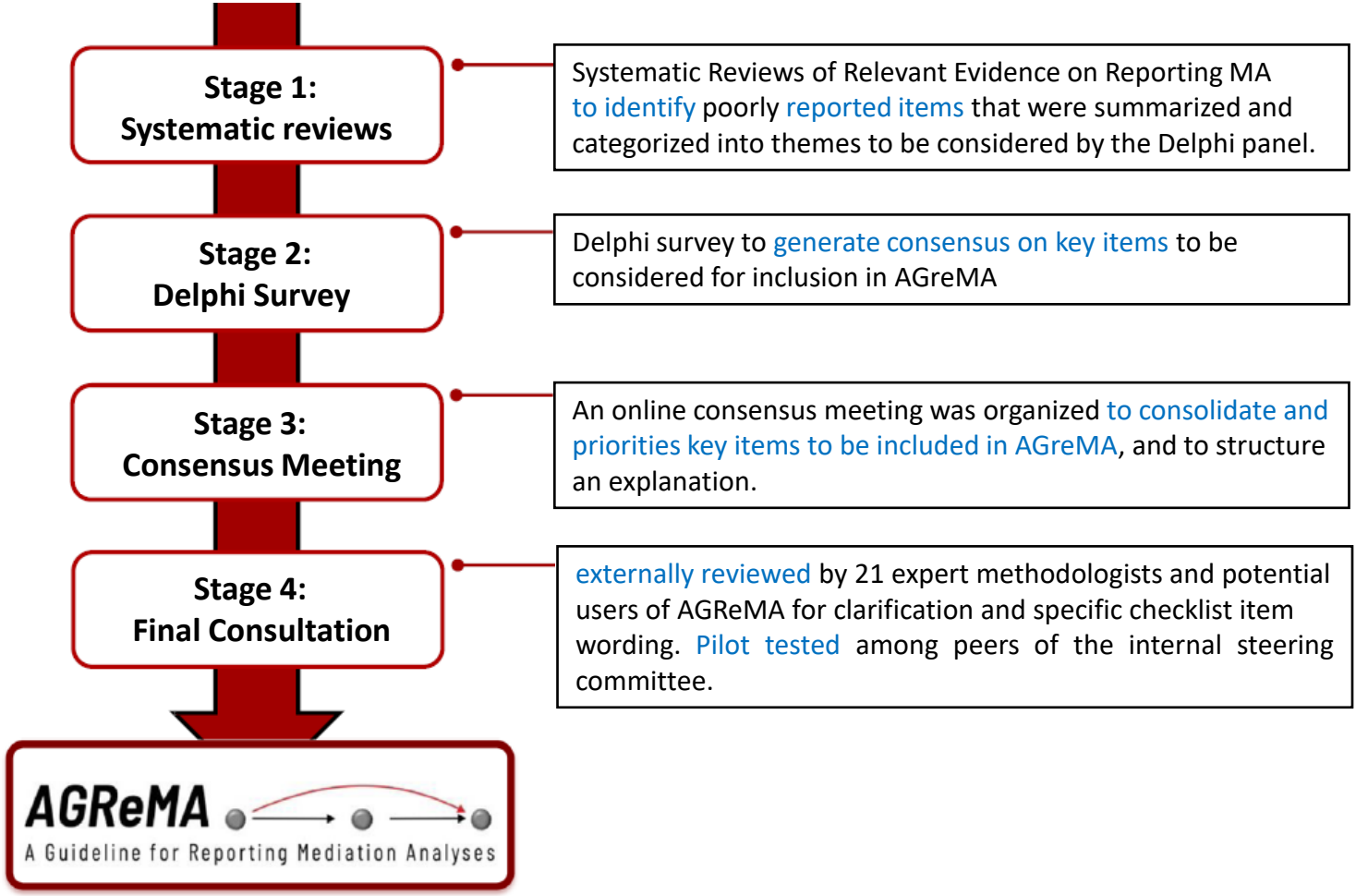
THE AGREMA STATEMENT

Workflow for the development of AGReMA:

followed the EQUATOR methodological framework



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THE AGREMA STATEMENT

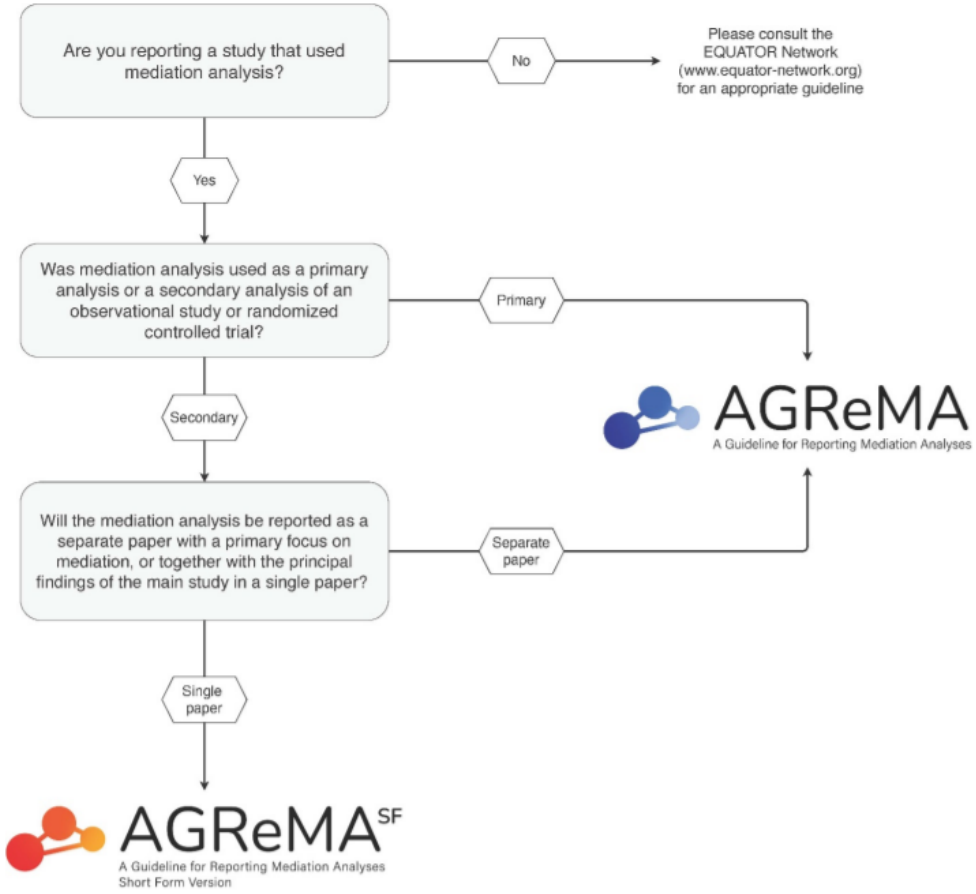
Checklist Items and Explanation

- **a 25-item AGReMA (full- form):** AGReMA — A Guideline for Reporting Mediation Analyses

  for reports that primarily focus on the results of MA.

- **a 9-item AGReMA short-form (AGReMASF):** AGReMA^{SF} — A Guideline for Reporting Mediation Analyses Short Form Version

  The AGReMA-SF is a subset of items from the standard checklist that were considered essential for reporting MA within reports of randomized trials or observational studies.



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AGReMA Statement

Section and topic	AGReMA A Guideline for Reporting Mediation Analyses 25-item (Full- form)	AGReMA SF A Guideline for Reporting Mediation Analyses Short Form Version 9-item (Short- form)
Title and abstract	☑	NA
Introduction	☑	☑
Methods	☑	☑
Results	☑	☑
Discussion	☑	☑
Other information	☑	NA

- Objectives
- Effects of interest
- Causal assumptions
- Measurement
- Statistical methods
- Participants
- Outcomes and estimates
- Limitation
- interpretation

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AGReMA
A Guideline for Reporting Mediation Analyses

Section and topic	Item No.	Item description
Title and abstract		
Title	1	• Identify that the study uses mediation analyses
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 mediation analyses 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 analytic 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 mediation analyses and the role of the funders/sponsors in the conduct of the study, writing of the manuscript, and decision to submit the manuscript 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 mediation analyses

AGReMA^{SF}
A Guideline for Reporting Mediation Analyses
Short Form Version

Table 2. A Guideline for Reporting Mediation Analyses Short-Form (AGReMA-SF) Checklist[a]

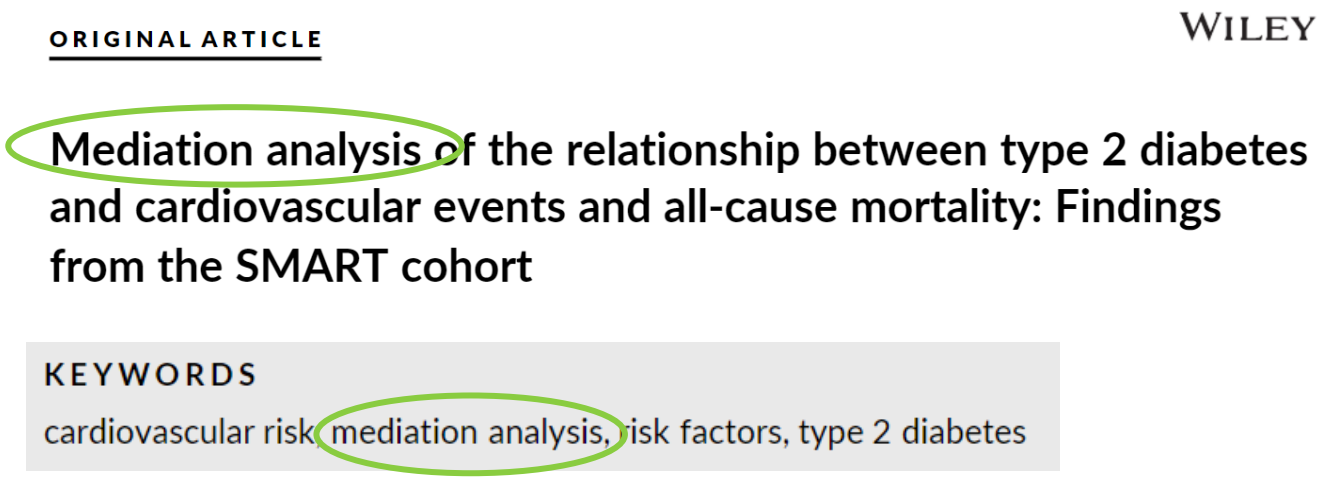
Section and topic	Item No.	Item description
Introduction		
Objectives	1	• State the objectives of the study, specific to the mechanisms of interest • The objectives should specify whether the study aims to test or estimate the mechanistic effects
Methods		
Effects of interest	2	• Specify the effects of interest
Causal assumptions	3	• Specify assumptions about the causal model
Measurement	4	• 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
Statistical methods	5	• Describe the statistical methods used to estimate the causal relationships of interest • This description should specify analytic 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 reference to the statistical software and package used
Results		
Participants	6	• 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	7	• 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
Discussion		
Limitations	8	• Discuss the limitations of the study including potential sources of bias
Interpretation	9	• 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

I: TITLE AND ABSTRACT

Item 1.

Title: Identify that the study uses mediation analyses in Title or as Keyword.

: such as *"mediation analysis, mediation,* or *mediator"*



ORIGINAL ARTICLE

WILEY

Mediation analysis of the relationship between type 2 diabetes and cardiovascular events and all-cause mortality: Findings from the SMART cohort

KEYWORDS

cardiovascular risk, mediation analysis, risk factors, type 2 diabetes

AGReMA

A Guideline for Reporting Mediation Analyses

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I: TITLE AND ABSTRACT

Item 1. **Title:** Identify that the study uses mediation analyses in Title.

Item 2. **Abstract:** Provide a summary of the objectives, methods, results, and conclusions specific to mediation analyses.

: objectives (supported by background/ rationale for the mechanisms of interest)
: methods (including the setting, participants, sample size, exposure, mediator, outcome, and analytic approach for mediation analyses)
: results (including point estimates and uncertainty estimates)
: main conclusion

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II: INTRODUCTION

Item 3.

Background and Rationale: Describe the study background/ rationale for investigating the mechanisms of interest.

: "why the intervention or exposure might affect the mediators"
"why the mediators might affect the outcomes"
"why mediation analyses helps to answer the substantive scientific question"

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II: INTRODUCTION

Item 3.

Background and Rationale: Describe the study background/ rationale for investigating the mechanisms of interest.

Item 4.

Objectives:**

State the objectives of the study specific to the mediation analysis (or mechanism of interests), whether using MA in primary or secondary objectives.

: Ex. should specify the aim is…

(1) to test the presence of an indirect or direct effect.
(2) to estimate the magnitude of an indirect or direct effect.
(3) to assess the magnitude of different pathways leading to the outcome (path-specific effects).

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III: METHODS

Item 5.

Study Registration: (If applicable),
provide references to any protocols or study registrations specific to MA and highlight any deviations from the planned protocol.

: the name of registration where the protocol was registered.
: the registration number

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III: METHODS

Item 6.

Study Design and Source of Data: Specify the design of the original study that was used in the mediation analyses and where the details can be accessed, supported by a reference.

- It is important for the mediation study to provide sufficient detail on study design.
  → RCTs or observational study

Note:

❖ Different study designs require different sets of assumptions for the estimation of indirect and direct effects in mediation analyses.

Such as

❖ RCTs: the intervention-mediator effects and the intervention-outcome effects are not confounded because of random allocation of the intervention.

❖ Observational studies: : the intervention-mediator effects, the intervention-outcome effects, and mediator-outcome effect might be confounded.

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III: METHODS(CONT.)

Item 7.

Participants:

: should be clearly describe → "target population/ eligibility criteria "
→ "study setting"
→ "study date/period (start of enrollment - end of follow-up)"

- Allow readers to determine whether the findings are generalizable to the target population of interest and assist systematic reviewers in assessing heterogeneity.

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III: METHODS(CONT.)

Item 7.

Participants:

: should be clearly describe → "target population/ eligibility criteria "
→ "study setting"
→ "study date/period (start of enrollment - end of follow-up)"

Item 8.

Sample Size: State whether a sample size calculation was conducted for the mediation analyses. If so, explain how it was calculated.

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III: METHODS(CONT.)

Item 9.

Effects of Interest:**

Depending on the research question and the study objectives.

→ it is recommended that authors link the objectives to the possible effects of interest. If aim to test more than 1 mediator effects, please clearly specify.

: Ex. exposure-mediator effect, mediator-outcome effect, direct or indirect effects or path-specific effects.

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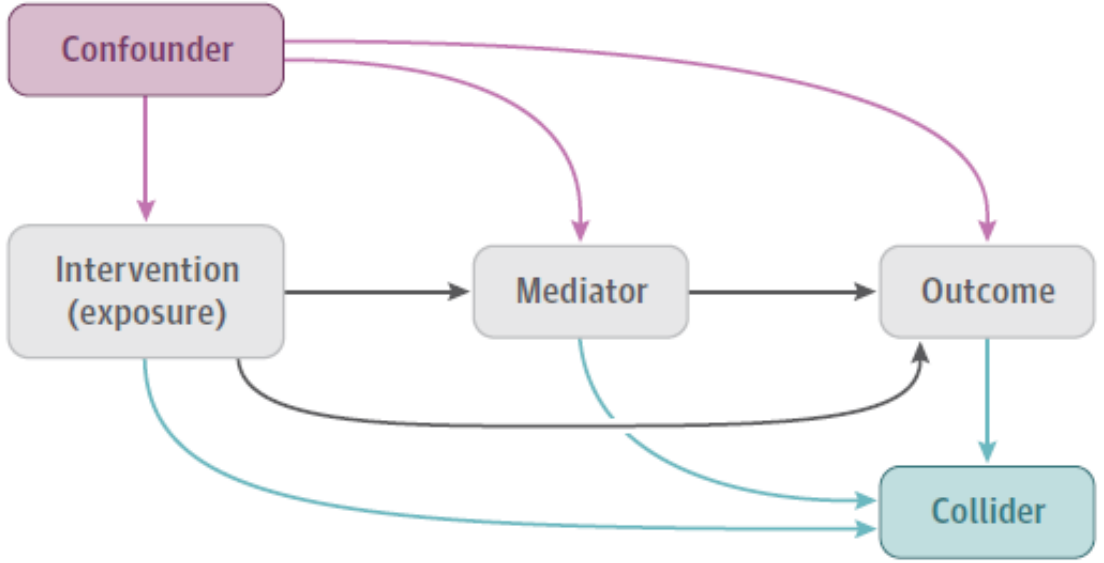
III: METHODS(CONT.)

Item 10.

Assumed Causal Model: Include a graphic representation of the assumed causal model including the exposure, mediator, outcome, and possible confounders.

- The causal model should be transparently described.
  because it can influence how MA are conducted, and influence results and interpretation.

- one practical method is using "Causal directed acyclic graphs" for MA



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III: METHODS(CONT.)

Item 11.

Causal Assumptions:**

Specify assumptions about the causal model

- It is important to be clear about the assumptions of a causal model.
  because they guide the analytic approach, expose possible sources of bias, and help determine the extent to which an estimate can be interpreted as a possible causal relationship.

"The assumptions should be discussed to avoid any misinterpretation of the findings"

For causal Inference approach,
there are important assumptions, which is about "Unmeasured confounders"

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III: METHODS(CONT.)

Item 11.

Causal Assumptions:**

Specify assumptions about the causal model

Such as…
: which unmeasured confounders are considered important.
(in the exposure-mediator, exposure-outcome, and mediator-outcome relationships)

: could guide the sensitivity analyses and allow the reader to determine how unmeasured confounders would influence the interpretation of the estimates.

AGReMA
A Guideline for Reporting Mediation Analyses

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III: METHODS(CONT.)

Item 12.

Measurement:**

Should clearly describe and specify…

- **What/Which:** the interventions or exposures, mediators, outcomes, confounders that were used in the analyses.

- **How and When:** they were measured, the measurement tools, and whether blinded assessment was used.

- Because measurement error can introduce bias in mediation analyses.
- it is important to report relevant measurement properties of the assessment that was used.

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III: METHODS(CONT.)

Item 13.

Measurement Levels:

If relevant, describe the levels at which the exposure, mediator, and outcome were measured.

Ex. In a cluster-randomized trial:

Researchers may study the effect of a hospital-level intervention on mediators and outcomes measured at the individual level. The data are considered multilevel or clustered.

Authors should describe how clustering was accounted for with regard to within- and between-cluster heterogeneity, for the estimation of direct and indirect effects.

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III: METHODS(CONT.)

Item 14.

Statistical Methods:**

Describe the statistical methods used to estimate the causal relationships of interest.

This description should specify

: the analytic approaches used to reduce confounding.
(product and difference-of-coefficients or Counterfactual-based approach)
: model building procedures, possible interaction,
: modeling assumptions
: the methods used to handle missing data.
: Provide a reference to the statistical software and package used.

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III: METHODS(CONT.)

Item 15.

Sensitivity Analyses:

Describe any sensitivity analyses that were used to explore *causal assumptions* (item 11), *statistical assumptions*, or both, and the influence of *missing data*.

Ex. **Causal assumptions:**
using sensitivity analyses
(such as **the E-value**) are used to explore **unmeasured confounders assumptions.**

→ To assume that there is no residual confounding of the E-M, E-O, and M-O relationships.

Ex. **statistical assumptions**
(regression model):

: how **model fit** was assessed?
: which **goodness-of-fit** assessment was used to assess?

Ex. **missing data:**
the results may vary depending on the imputation method.

: what sensitivity analyses used to assess the method of handling missing data should be reported.
(such as **bootstrap)**

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III: METHODS(CONT.)

Item 16.

Ethical Approval:

Name the institutional research board or ethics committee that approved the study and provide a description of participant informed consent or an ethics committee waiver of informed consent.

- This may be approval for the original randomized trial or observational study, or a separate approval for the mediation analyses.

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IV: RESULTS

Item 17.

Participants:**

Should…

- Describe the baseline characteristics of the participants included in the mediation analyses
  → likely it is for selection bias to influence the results.
- Report the total sample size
- Report the number of participants lost during follow-up or with missing data for the mediators, outcomes, and possible confounders.

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IV: RESULTS (CONT.)

Item 18.

Outcomes and Estimates:**

Report point estimates and uncertainty estimates (95% CI, SE, SD)

- direct and/or indirect effects along with their standard errors or 95%CIs .

(e.g., mean difference, risk difference, RR, OR, HR: depends on objectives)

Ex. The indirect effect of intensive BP therapy on CVD events mediated through low diastolic BP had a HR of 1.12 [95% CI, 1.06 to 1.18]

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IV: RESULTS (CONT.)

Item 19.

Sensitivity Parameters：

Report the results from any sensitivity analyses used to assess the robustness of causal assumptions, statistical assumptions, or both, and the influence of missing data.

This will help readers judge the robustness of the findings.

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IV: DISCUSSION

Item 20.

Limitations:**

Authors should state any limitations and comment on how they might affect the validity of the main findings. If a sensitivity analysis was used to explore the effect of a limitation, the results should be discussed considering the main findings.

such as failure to account for unmeasured confounding, measurement error, model misspecification, selection bias, and missing data.

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IV: DISCUSSION

Item 21.

Interpretation:**

Interpret the estimated effects considering their magnitude and uncertainty, the causal assumptions, limitations, generalizability of the findings, and results from relevant studies.

- This will depend on how reasonable the causal assumptions are (item 11), possibly supplemented with results from sensitivity analyses (item 19) and other limitations (item 20).
- The interpretation should also be set in the context of any previously identified theoretical or evidence-based rationale for mediation analyses.
- The generalizability of the overall findings should also be discussed to guide the application of the findings into clinical practice, if appropriate.

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IV: DISCUSSION

Item 22.

Implications :

Discuss the implications of the overall results for clinical practice, policy, and science.

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V: OTHER INFORMATION

Item 23.

Funding and Role of Sponsor :

List all sources of funding or sponsorship and the role of the funders/sponsors in the conduct of the study, writing of the manuscript, and decision to submit the manuscript for publication.

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V: OTHER INFORMATION

Item 24.

Conflicts of Interest and Financial Disclosures:

State any conflicts of interest and financial disclosures for all authors

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V: OTHER INFORMATION

Item 25.

Data and Code:

Authors are encouraged to provide a statement for sharing data and code for mediation analyses. If possible, data should be shared in an accessible, secure, and reliable database

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DISCUSSIONS

- The AGReMA statement provides international consensus-based guidance on items that should be reported in studies that use mediation analyses.
- The scope of the AGReMA statement covers primary and secondary mediation analyses of randomized trials and observational studies, and it is intended to be general so that it can guide the reporting of most mediation analyses.
- Should be interpreted with caution in both observational designs and randomized trials because causal assumptions may be unmet and it may not be possible to establish causal inferences.

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DISCUSSIONS

- The purpose of theAGReMA statement is to improve completeness, consistency, and accuracy in reporting. It is not designed to guide conduct or to be used as a risk of bias tool.
- To improve accessibility, the AGReMA checklists will be made available on an open web domain (https://agrema-statement.org) and indexed in the EQUATOR Network website.

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LIMITATIONS

- First, participants of the Delphi process and consensus meetings were purposefully selected based on expertise and familiarity with mediation analyses and scientific reporting.
- Second, approaches to mediation analyses are grounded in 2 distinct traditions.
- Third, because of travel and social contact restrictions from the COVID-19 pandemic, the consensus meeting was conducted online rather than face-to-face. Smaller group discussions also took place after the 2-day meeting.

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CONCLUSIONS

- The AGReMA statement provides recommendations for reporting primary and secondary mediation analyses of randomized trials and observational studies.
- Improved reporting of studies that use mediation analyses could facilitate peer review and help produce publications that are complete, accurate, transparent, and reproducible.

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Thank You!