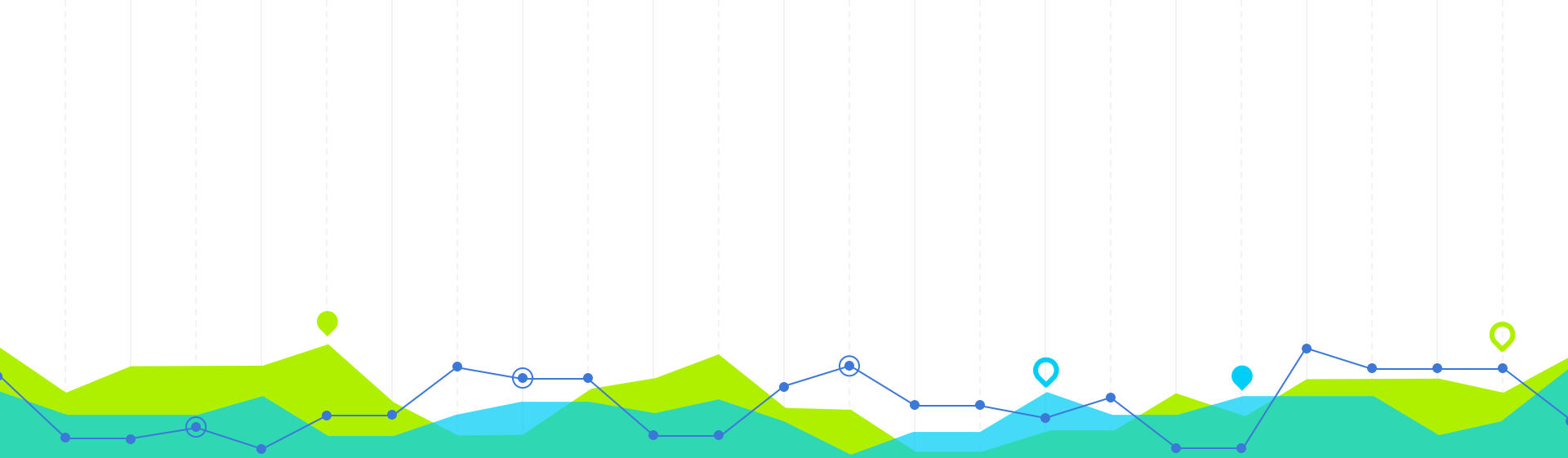# A REPORTING GUIDELINE FOR MEDIATION ANALYSIS

Amarit Tansawet

The AGReMA Statement

Introduction & Methods

1

Objectives of AGReMA project

◉ A Guideline for Reporting Mediation Analyses = AGReMA

◉ to develop an evidence- and consensus-based reporting guideline

◉ to produce a long and short form to support primary or secondary reports of mediation analyses
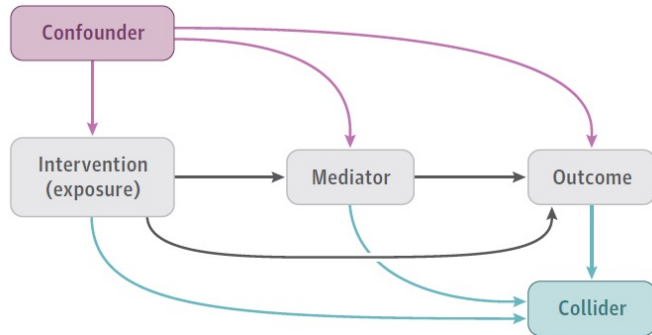
Terminology

Mediation analysis: An empirical method used to explain how an exposure causes an outcome.

Mechanism: The causal process by which an exposure causes an outcome.

Action Theory: A theory that supports the hypothesized relationship between an intervention or an exposure and a given mediator.

Conceptual theory: A theory that supports the hypothesized relationship between a mediator and a given outcome.

Disjunctive cause criterion: A criterion that recommends adjusting for all covariates that are causes of the exposure, outcome, or both when the underlying causal structure is unknown and only limited knowledge is available.

Terminology

◉ **Collider:** a variable that is caused by the intervention or exposure and mediator, by the intervention or exposure and outcome, or by the mediator and outcome. Conditioning on a collider by design or analysis may induce selection bias.

◉ **Confounder:** a variable that causes the intervention or exposure and mediator, the intervention or exposure and outcome, or the mediator and outcome. Uncontrolled confounders can induce confounding bias.

◉ **Mediator:** A variable that may be affected by an exposure and may in turn affect an outcome.

◉ **Moderator:** A variable that alters the direction or magnitude of the effect of an exposure on an outcome.
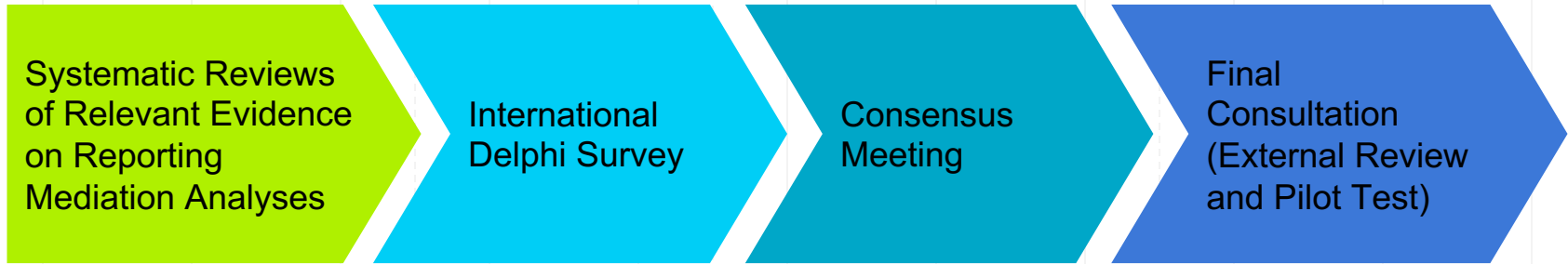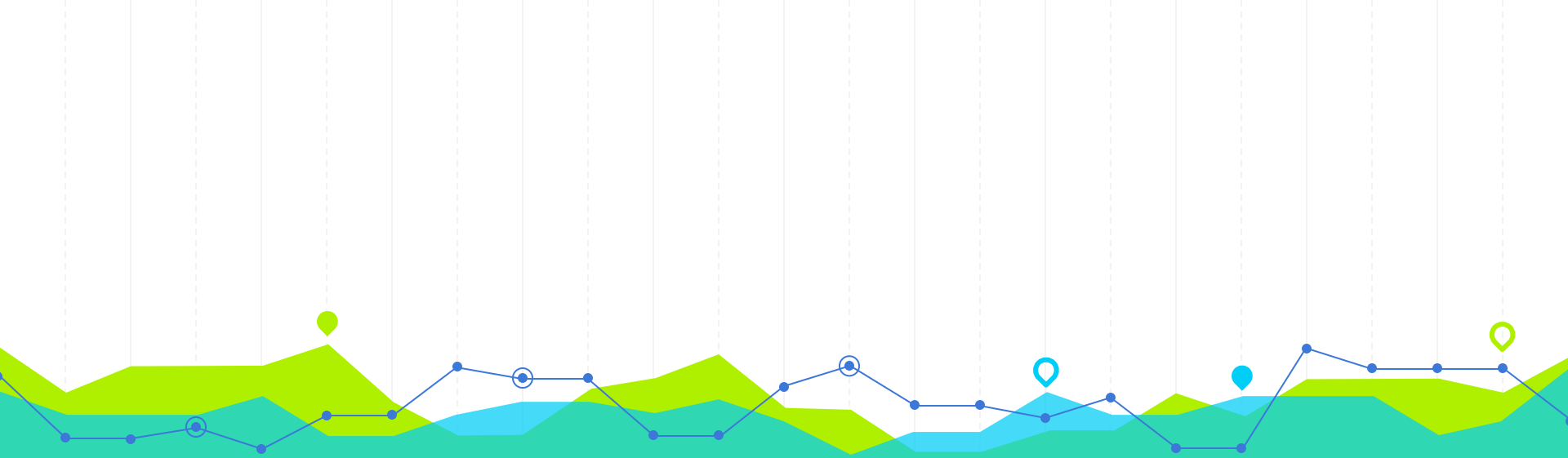
Terminology

- Causal directed acyclic graph

- Natural direct effect: The exposure's effect on the outcome if a given mediator were fixed at its natural value

- Controlled direct effect: The exposure's effect on the outcome if a given mediator were fixed at a constant level uniformly across the entire study population.

- Natural indirect effect: An effect on the outcome that is caused by the exposure's effect on a given mediator and that mediator's subsequent effect on the outcome.

- Total effect: The entire effect of the exposure on the outcome that encompasses all indirect and direct effects.

- Path-specific effect: An effect that captures how much of the exposure's effect on a given outcome is mediated through intermediate variables along 1 or multiple pathways.

- Spillover effect: When the outcome of a participant in a study is affected by the intervention status of other participants in the same study.

PROCESS

Systematic Reviews of Relevant Evidence on Reporting Mediation Analyses

International Delphi Survey

Consensus Meeting
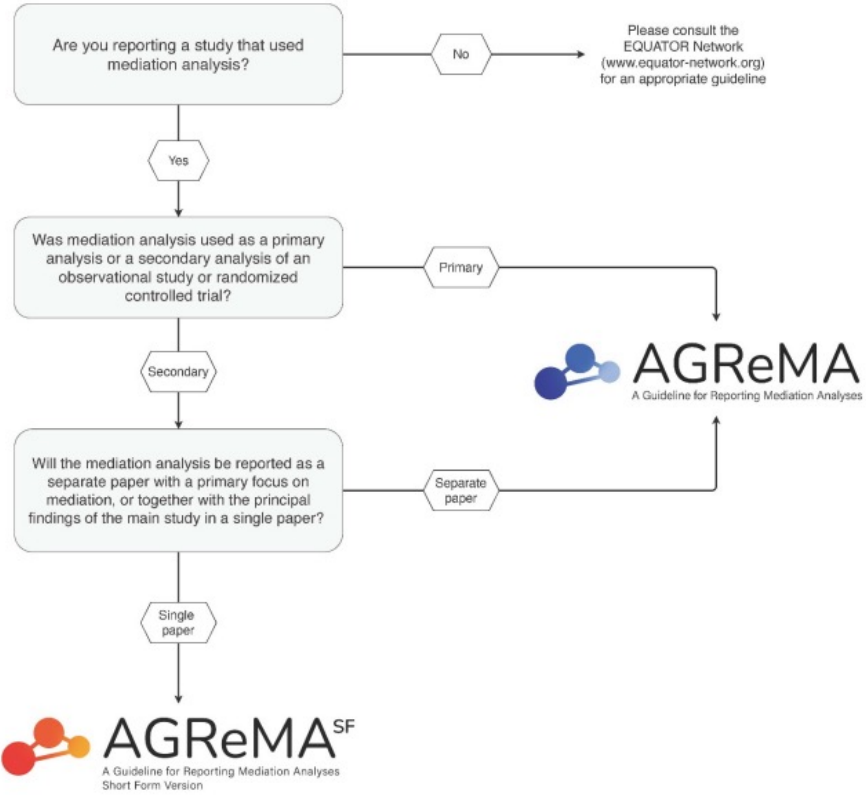
Final Consultation (External Review and Pilot Test)

Checklist items & Explanation

2

Item 1 (title & abstract)

◉ Title

◉ Identify that the study uses mediation analyses

◉ Including terms such as *mediation analysis*, *mediation*, or *mediator* in the title or as keywords

Item 2 (title & abstract)

- Abstract

- Provide a structured summary of the objectives, methods, results, and conclusions specific to mediation analyses.

- objectives ideally supported by a brief statement of background and rationale for the mechanisms of interest

- analytic approach for mediation analyses

Item 3 (introduction)

- Background and Rationale

- Describe the study background and theoretical rationale for investigating the mechanisms of interest.

- Include supporting evidence or the theoretical rationale for why the intervention or exposure might affect the proposed mediators and why the mediators might affect the outcomes.

- make clear why mediation analyses helps to answer the substantive scientific question.

- Describing the theory that underpins the proposed mechanisms of interest (action & conceptual theory)

- Rationale should be supported with empirical or qualitative evidence

Item 4 (introduction)

- objective

- 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.

- The objectives should specify whether the aim is (1) to test the presence of an indirect or direct effect or (2) to estimate the magnitude of an indirect or direct effect.

- declare whether the aim of mediation analyses is explanatory (to explain what mediates a causal relationship) or interventional (to ask questions about possible causal mechanisms of hypothetical interventions that target the exposure or mediator).

Item 5 (methods)

- Study registration

- If applicable, provide references to any protocols or study registrations specific to mediation analyses and highlight any deviations from the planned protocol.

Item 6 (methods)

- 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.

- If applicable, describe study design features that are relevant to mediation analyses.

- it is important to provide a clear description of the original study design and data sources so the potential risks of bias can be assessed.

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

Item 7 (methods)

◉ Participants

◉ Describe the target population, eligibility criteria specific to mediation analyses, study locations, and study dates (start of participant enrollment and end of follow-up).

Item 8 (methods)

◉ Sample size

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

◉ E.g., the effect of the exposure on the mediator and residual mediator variance, the effects of the exposure and the mediator on the outcome and residual outcome variance, significance level, and desired power
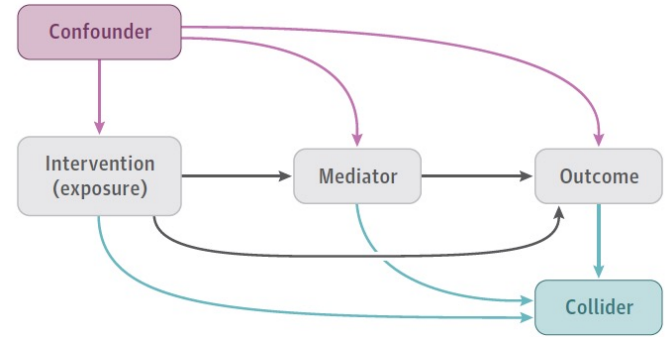
Item 9 (methods)

◉ Effects of interest

◉ Specify the effects of interest.
- ◉ exposure-mediator effect
- ◉ mediator-outcome effect
- ◉ controlled direct effect
- ◉ natural direct and indirect effects
- ◉ interventional direct and indirect effects
- ◉ path-specific effects.

◉ Because the chosen effect of interest will require a specific set of assumptions, drive the analytic method, and guide interpretation

◉ Multiple objectives and effects of interest >> link the study objectives to the possible effects of interest

Item 10 (methods)

- Assumed causal model

- Include a graphic representation of the assumed causal model including the exposure, mediator, outcome, and possible confounders.

Item 11 (methods)

◉ Causal assumption

◉ Specify assumptions about the 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.

◉ Clearly outlining the temporal precedence of the variables in a mediation model is also important for assessing the direction of hypothesized causal relationships and the possibility of reverse causation.

Item 12 (methods)

- Measurement

- 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.

Item 13 (methods)

- Measurement levels

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

- In a cluster-randomized trial, authors should describe whether the exposures, mediators, and outcomes were assigned or measured at the group or individual level.

- describe how clustering was accounted for with regard to within- and between-cluster heterogeneity, and possible spillover effects if relevant, for the estimation of direct and indirect effects.

Item 14 (methods)

◉ Statistical methods

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

◉ This description should specify the analytic strategies used to reduce confounding, model building procedures, justification for the inclusion or exclusion of possible interaction terms, modeling assumptions, and the methods used to handle missing data.

◉ Provide a reference to the statistical software and package used

Item 14 con. (methods)

- 2 major traditions for conducting mediation analyses:
  - those deriving from the causal steps of Baron and Kenny or with a product and difference-of-coefficients framework
  - those from the counterfactual-based framework
- Authors should report how confounders were identified, for example, through the use of causal directed acyclic graphs, the disjunctive cause criterion, or when data-driven, use of variable selection procedures such as stepwise testing strategies or penalization methods in models for the mediator and outcome.

Item 14 con. (methods)

◉ should clearly report the functional form and specification of the regression models that were used to model the mediators and outcomes and report any modeling assumptions that were made.

◉ If a variable selection procedure was used or if interactions were modeled to improve model flexibility, authors should report these so that readers can assess the appropriateness of the models that eventually inform the estimation of the direct and indirect effects.

◉ state whether the data were imputed and, if so, report detailed information about the selected method for handling missing data.

Item 15 (methods)

- Sensitivity analyses

- Describe any sensitivity analyses that were used to explore causal assumptions, statistical assumptions, or both, and the influence of missing data.

Item 16 (methods)

◉ 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.

Item 17 (Results)

◉ Participants

◉ Describe the baseline characteristics of the participants included in the mediation analyses and report the total sample size and the number of participants lost during follow-up or with missing data.

◉ Reporting how the baseline characteristics of those lost to follow-up or with missing data compared with the participants analyzed can provide readers with a sense of how likely it is for selection bias to influence the results.

◉ It may not be sufficient to describe only the overall participants included in the primary study because the variables required for the mediation analyses may have been collected only in a subsample of the primary study sample

Item 18 (Results)

◉ Outcomes and estimates

◉ 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.

Item 18 con (Results)

- In most cases, the natural direct and indirect effects are recommended when the aim is to explain the causal relationship between an exposure and an outcome through 1 or more mediators

- If the study objective is to estimate the causal relationship between an exposure and an outcome while a mediator is fixed at a constant level uniformly across the population, the controlled direct effect is recommended

- When the necessary causal assumptions are thought to be plausible, authors should report unstandardized estimates, standardized estimates, or both, of direct and indirect effects

Item 19 (Results)

◉ 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.

Item 20 (Discussion)

◉ Limitations

◉ Discuss the limitations of the study, including potential sources of bias.

Item 21 (Discussion)

◉ Interpretation

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

◉ An important aspect of interpreting estimates from mediation analyses is appraising whether the estimate can have a possible causal interpretation.

◉ This will depend on how reasonable the causal assumptions are, possibly supplemented with results from sensitivity analyses, and other limitations

Item 22 (Discussion)

◉ Implication

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

Item 23 (Other information)

◉ Funding and role of sponsor

◉ 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.

Item 24 (Other information)

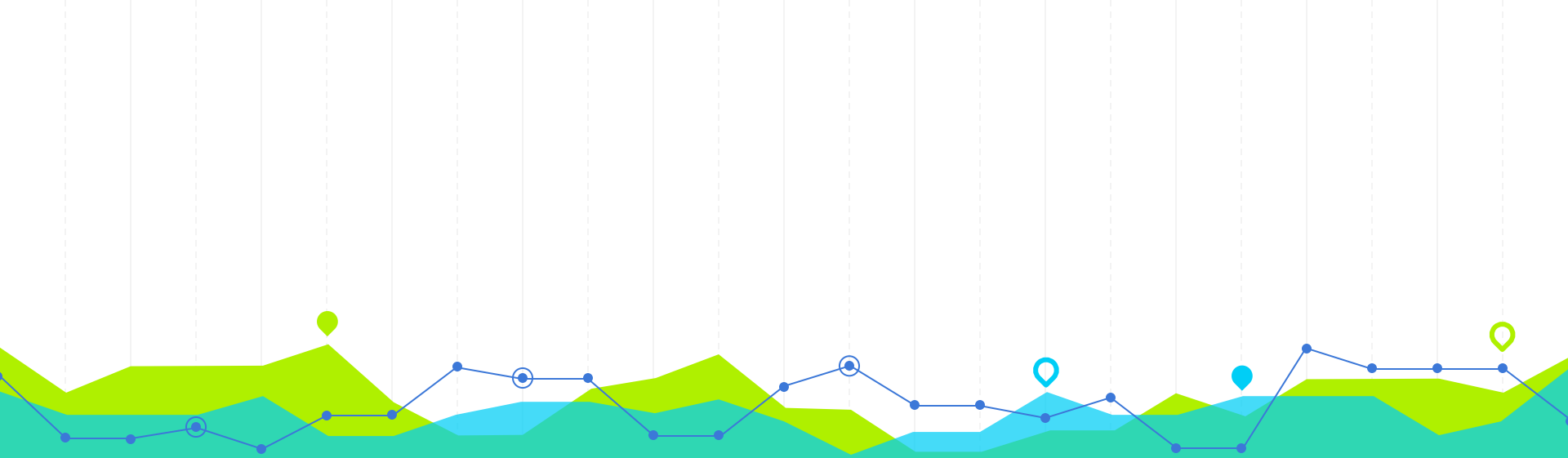◉ Conflicts of Interest and Financial Disclosures

◉ State any conflicts of interest and financial disclosures for all authors.

Item 25 (Other information)

◉ Data and code

◉ Authors are encouraged to provide a statement for sharing data and code for mediation analyses.
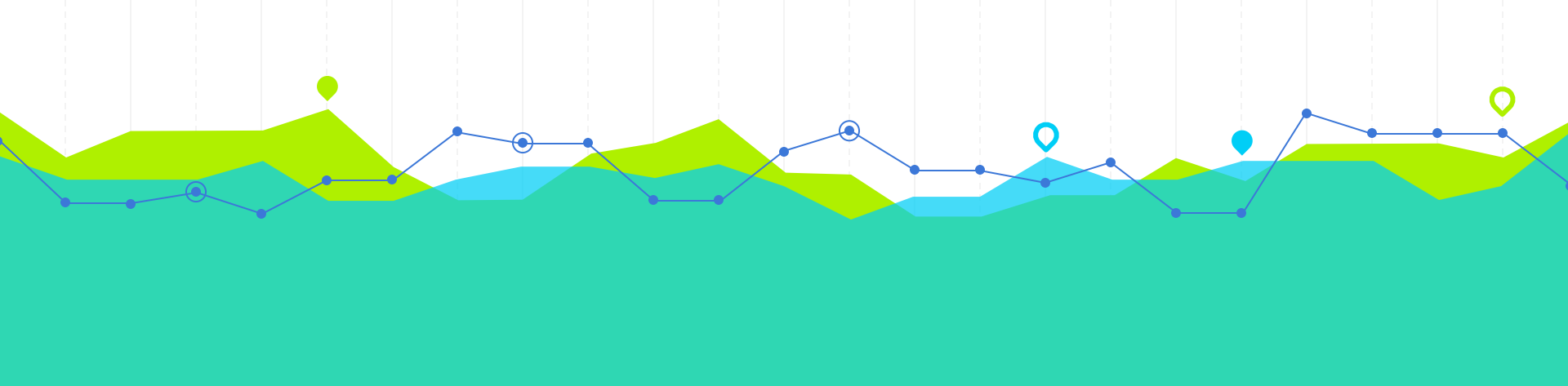
Table 2. A Guideline for Reporting Mediation Analyses Short-Form (AGReMA-SF) Checklist[a]

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

Conclusion

3

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.

THANKS!

Any questions?