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COMMENTARY

An introduction to mediation analyses of randomized controlled trials

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Abstract

Mediation analyses of randomized controlled trials can be used to investigate the mechanisms by which health interventions cause outcomes. In this article we provide a brief introduction to mediation analysis in the context of randomized controlled trials. We introduce common target effects, causal assumptions, estimation approaches, and illustrate these concepts using a published mediation analysis of the Systolic Blood Pressure Intervention Trial. Well-conducted mediation analyses of randomized trials can provide meaningful insights to guide clinical and policy decisions.

Keywords: Mediation analysis; Mechanism; Randomised controlled trial

1. Introduction

Randomized controlled trials (RCTs) are primarily used to answer questions about the efficacy and effectiveness of health interventions. For health interventions that are expected to have their effects on outcomes through a causal mechanism, mediation analysis can be used to partition the total effect of an intervention into an indirect effect, which operates through a selected mechanism of interest, and a direct effect which operates through all other mechanisms [1]. Well-conducted mediation analyses can guide the optimization and implementation of health interventions and policies. International funding agencies such as the US National Institutes of Health and the UK National Institute for Health Research have highlighted the importance of understanding how interventions work through the use of mediation analyses.

Methods for mediation analysis have been available for decades. Recent advances in mediation analysis have outlined necessary assumptions that are required to make valid causal inferences about indirect and direct effects [1]. This approach to mediation has also produced methods that can accommodate more realistic settings where there may be intervention–mediator interactions, non-linear relationships, and interest in multiple and sequenced mediating pathways. In this article, we provide a brief introduction to mediation analysis within the context of RCTs. We illustrate key concepts using a published mediation analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) [2].

2. Target effects

Mediation analysis can be used to estimate indirect and direct effects of interventions. With mediation analysis, the total effect of an intervention on an outcome can be decomposed into a natural indirect and natural direct effect. In a general sense, the natural indirect effect encapsulates the effect of an intervention on an outcome that operates through a selected mediator; whereas the natural direct effect encapsulates the effect of an intervention on an outcome that does not operate through the selected mediator (through other mechanisms). These target effects are described in greater detail in Table 1 and Fig. 1. Nguyen et al. [3] provide a lucid explanation of relevant target effects that can be estimated using mediation analysis.

3. Assumptions for making valid causal inferences from mediation analyses

There are several important methodological considerations and causal assumptions that must be met to interpret indirect and direct effects as causal effects.

Conflicts of interest: None.

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Table 1. Common target causal effects in mediation analysis

Target effect	Definition*	Example
Total effect	The average difference in the outcome between individuals allocated to the intervention versus control groups	The effect of intensive therapy versus standard therapy on cardiovascular events
Intervention–mediator effect	The average difference in the mediator between individuals allocated to the intervention versus control groups	The effect of intensive therapy versus standard therapy on diastolic blood pressure
Mediator–outcome effect	The average difference in the outcome across different levels of the mediator	The effect of diastolic blood pressure on cardiovascular events
Natural indirect effect	The average difference in the outcome caused by the average effect of the intervention on the mediator	The effect of intensive therapy versus standard therapy on cardiovascular events that is caused by its effect through diastolic blood pressure
Natural direct effect	The average difference in the outcome caused by the intervention while the mediator is held to its natural level under the control or the intervention	The effect of intensive therapy versus standard therapy on cardiovascular events when diastolic blood pressure is held at its natural value, defined as the value it would take under the standard therapy (or intensive therapy)
Controlled direct effect	The average difference in the outcome caused by the intervention while the mediator is held at a constant level across the entire study population	The effect of intensive therapy versus standard therapy on cardiovascular events when diastolic blood pressure is held at a constant level, uniformly across the entire study sample

* For simplicity, the definitions assume a binary intervention and a continuous mediator and outcome.

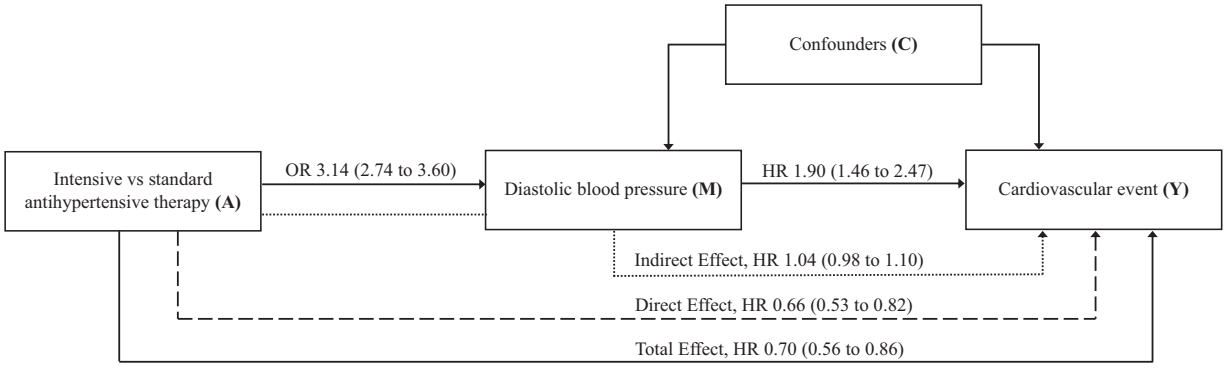

Fig. 1. A causal diagram depicting the effects in a mediation analysis of the SPRINT trial [2]. The total effect is represented by the solid arrow from A to Y. The intervention–mediator effect is represented by the solid arrow from A to M. The mediator–outcome effect is represented by the solid arrow from M to Y. Confounding of the mediator–outcome effect is represented by the solid arrows from C to M and C to Y. The dotted arrow from A to Y via M represents the indirect effect. The dashed arrow from A to Y represents the direct effect. There can be variations of the direct effect as described in Table 1. All estimates are presented with 95% confidence intervals. OR, odds ratio; HR, hazard ratio.

3.1. Temporal sequence of interventions, mediators, and outcomes

The temporal sequence of the intervention, mediator, and outcome should be considered in the interpretation of indirect and direct effects. In the context of RCTs, it is mostly guaranteed that the mediator and outcome are measured after assignment to interventions. Therefore, the only requirement is for the mediator to be measured before the outcome. However, in some instances it may be clear that the mediator precedes the outcome event without temporal sequencing of measurements, for example, if a cointervention is a mediator and death is an outcome.

3.2. Exchangeability (no unmeasured confounding)

Exchangeability in the context of mediation analysis requires that there are no unmeasured confounders of the intervention–mediator, intervention–outcome, and mediator–outcome effects. In addition, there must not be any mediator-outcome confounders that are affected by the intervention. In most RCTs, we can assume that the intervention–mediator and intervention–outcome effects are unconfounded because of random allocation of participants. However, random allocation of the intervention does not prevent confounding of the mediator-outcome effect. Thus, careful selection, measurement and adjustment for mediator-outcome confounders is essential in me-

diation analyses of RCTs, while also ensuring that those confounders are not affected by the intervention. Sensitivity analyses can be used to assess the robustness of indirect and direct effects, subject to possible violations of the exchangeability assumption due to residual confounding.

3.3. Consistency and positivity

As with any causal analysis, mediation analysis requires the intervention and mediators to be well-defined (consistency), and there be a non-zero probability for any participant to enter the intervention/control groups and exhibit any level of the mediator (positivity) [1]. Nguyen et al. [4] provide an accessible explanation of these assumptions.

4. Estimation

If the casual assumptions seem tenable, there are several strategies for estimating indirect and direct effects. Often mediation analyses will rely on two working models. One that treats the mediator as the dependent variable, and another that treats the outcome as the dependent variable. Most estimation strategies will use parameters from these working models to make predictions about unobserved potential outcomes. These predicted potential outcomes are then combined with observed potential outcomes to estimate the target effects of interest. There are various software packages available, each with their own estimation strategies and programmatic capabilities. Valente et al. [7] provide a comprehensive summary of available software packages for mediation analysis.

5. Example: mediation analysis of the SPRINT trial

The SPRINT trial compared the effects of intensive antihypertensive therapy versus standard antihypertensive therapy on cardiovascular events in 9361 patients aged over 50 years. The primary hypothesized mechanism of antihypertensive therapy was that it would reduce systolic blood pressure (SBP) and thereby reduce the risk of cardiovascular events. In this trial, there was concern that the intensive therapy would also reduce diastolic blood pressure (DBP) alongside SBP; and this unintended effect on DBP would inadvertently increase the risk of cardiovascular events. To investigate the mediating role of DBP, the investigators conducted a causal mediation analysis (Fig. 1). First, the authors estimated the association between randomization and DBP (intervention–mediator effect, odds ratio 3.14 [95% confidence interval (CI) 2.74 to 3.60]), and the association between DBP and cardiovascular events (mediator-outcome effect, hazard ratio (HR) 1.90 [95% CI 1.46 to 2.47]). Second, the authors conducted a mediation analysis to estimate the effect of randomization on cardiovascular events through its effect on DBP (natural indirect effect), adjusting for mediator-outcome confounders. This analysis showed that intensive therapy induced reductions in DBP did not increase cardiovascular risk (natural indirect effect, HR 1.04 [95% CI 0.98 to 1.10]). Although low DBP itself is associated with an increased risk of cardiovascular events, these results suggested that this increased risk cannot be attributed to an unintended effect of intensive antihypertensive therapy on DBP.

6. Conclusion

Mediation analyses can extend the utility of RCTs by investigating the mechanisms by which interventions cause outcomes. Advances in methods have made it possible to apply mediation analyses to more complex settings such as failure-time outcomes, multi-level or clustered RCTs, multiple mediator models, and time-varying interventions and mediators [1]. To ensure adequate reporting and appraisal of mediation analyses, reporting guidelines [5] and risk of bias assessment tools are being developed. Where possible, trialist should plan mediation analyses in advance to ensure mediators and possible mediator-outcome confounders are measured. When mediation analyses are well-planned and conducted in the context of RCTs, they can provide useful information for optimizing and implementing interventions and policies.

CRediT authorship contribution statement

Aidan G. Cashin: Conceptualization, Methodology, Writing - original draft. **Hopin Lee:** Conceptualization, Methodology, Writing - original draft.

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