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EDITORIAL COMMENT

What Is Mediation Analysis?

Linking Exposures and Outcomes Through Intermediary Mechanisms*

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Both randomized controlled trials and observational research facilitate understanding of exposure-outcome relationships and help in optimizing care for patients with cardiovascular disease.[1,2] However, both designs have limitations in their ability to characterize intermediate mechanisms linking exposures and outcomes. Understanding such mechanisms is important for establishing biological plausibility, identifying potential treatment targets, anticipating potential off-target effects of therapy, and helping identify patient subgroups in whom the greatest benefit of a particular treatment may be accrued. Mediation analysis may augment randomized controlled trials and observational designs by querying candidate mechanistic links between exposures and outcomes and assessing whether the association between an exposure and outcome is mediated by the putative intermediate mechanism.[3,4] We refer the interested reader to dedicated textbooks and reviews that have been published elsewhere.[3,5,6]

In this issue of *JACC: Advances*, Hidaka et al[7] present a cohort study to evaluate the association between the blood biomarker fibroblast growth factor (FGF)-23 and clinical outcomes among adult patients with chronic kidney disease. The authors report that higher levels of FGF-23 are associated with higher left ventricular mass and increased risk for adverse clinical outcomes including all-cause mortality, atrial fibrillation, and congestive heart failure (relative to patients with lower levels). Interestingly, in mediation analysis, most of the association between FGF-23 and clinical outcomes was not mediated by left ventricular mass, suggesting that FGF-23 may be linked with these adverse outcomes through other mechanisms.

The authors should be congratulated on performing this comprehensive and thought-provoking study. Further, the study highlights the potential for mediation analysis to elucidate underlying mechanisms as well as several of the most common limitations and drawbacks. We anticipate that readers of the medical literature will increasingly encounter mediation analyses, and therefore a framework for interpretation would be useful. Accordingly, we summarize herein the main aspects of mediation analysis with the necessary assumptions and highlight several recent exemplar applications in cardiovascular research.

Causal mediation analysis seeks to uncover different mediator pathways between an exposure and outcome of interest (**Figure 1**); a mediator can be thought of as a variable that lies within the causal pathway and links the exposure and outcome. Hence, pathways between exposure and outcome may include the so-called: 1) direct effect (ie, not through the mediator); 2) indirect effect (ie, through the mediator); and 3) total effect (ie, the combination of both the direct and indirect effect).[3] Once these pathways are estimated, several measures (such as the percent of the association mediated by that particular variable) can be quantified. Several methods have been developed to estimate such quantities (eg,

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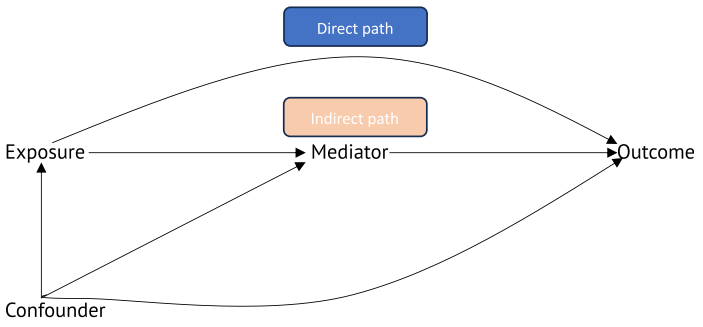
FIGURE 1 Conceptual Model



The figure illustrates the main elements of a mediation analysis. The sum of the direct and indirect paths would correspond to the total effect of the exposure on the outcome. Mediation analyses assume a temporal order, with the exposure (treatment) preceding the mediator and the mediator preceding the outcome. Additionally, mediation analyses assume that there is no unmeasured confounding between: 1) the exposure and the outcome, and 2) the exposure and the mediator, which are both automatically satisfied in a clinical trial setting. Mediation analyses also assume 3) no unmeasured confounding between the mediator and the outcome, and 4) no confounders between the mediator and the outcome that are affected by the exposure. These last 2 assumptions might be violated even when the exposure was randomized (clinical trials) and rely on content expertise related to the clinical question under investigation.

product and difference methods); additional considerations need to be taken depending on the measure of association used (eg, risk ratios vs odds ratios) and whether the outcome is common or infrequent.[5]

Researchers and practitioners need to be attentive to several required assumptions. Estimating direct and indirect effects generally requires a larger set of assumptions than the (common) estimation of total effects. These assumptions include no confounding of the: 1) exposure-mediator; 2) mediator-outcome; and 3) exposure-outcome relationships.[3,6] The extent to which the chosen potential confounders are sufficient depends solely on subject matter knowledge. Since this "lack of confounding" cannot generally be expected—and is otherwise assumed—in observational studies, performing mediation analysis within randomized trials (where at least baseline exchangeability between exposed and unexposed groups is expected) is considered more rigorous.

The study by Hidaka and colleagues deploys causal mediation analysis in an observational cohort. First, the authors identify a significant association of FGF-23 with all-cause death (ie, total effect; HR: ~1.68). Second, when evaluating different pathways, the direct pathway (ie, not through left ventricular mass) accounted for most of this association, with the hazard ratio for the indirect effect (through left ventricular mass) close to the unit (~1.03). In other words, left ventricular mass mediated only 7% of the effect of FGF-23 on all-cause mortality. Similar findings were reported for other outcomes of interest. The somewhat surprising lesser role of left ventricular mass in the pathway between FGF-23 and cardiovascular outcomes may not only improve understanding of mechanisms of cardiovascular disease pathogenesis in chronic kidney disease but also inform potential therapeutic strategies. However, readers should be mindful that such conclusions rely on a larger set of assumptions than the reported (total) association between FGF-23 and clinical outcomes. We refer the readers to several recent articles also deploying causal mediation analysis in cardiovascular research.[7-10] Notable examples showcase the potential mediators underlying, for example, the association between education or income with major cardiovascular disease in adult patients.

Overall, the findings by Hidaka may inform future avenues for research seeking to improve heart function-related outcomes in patients with chronic kidney disease. Their findings also exemplify the utility of deploying mediation analysis as a tool to interrogate mechanism. The depiction of such underpinnings remains paramount if we are to continue improving our understanding of the pathophysiology and treatment of cardiovascular disease.

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REFERENCES

1. Hernán M. Strengthening causal inference from observational data. *N Engl J Med*. 2021;385:1345-1348.
2. Rothman KJ, Greenland S. Causation and causal inference in epidemiology. *Am J Public Health*. 2005;95:144-150.
3. VanderWeele TJ. Mediation analysis: a practitioner's guide. *Annu Rev Public Health*. 2016;37:17-32.
4. Redfors B, Lin SH. Mediation analysis – an underused approach to cardiovascular research. *Coron Artery Dis*. 2020;31:620-622.
5. VanderWeele TJ. *Explanation in Causal Inference*. Oxford University Press; 2015.
6. VanderWeele TJ. Explanation in causal inference: developments in mediation and interaction. *Int J Epidemiol*. 2016;45:1904.

7. Hidaka N, Inoue K, Kato H, et al. FGF-23, left ventricular hypertrophy, and mortality in patients with CKD: a revisit with mediation analysis. *JACC: Adv*. 2024;3:100747.

8. Dondo TB, Hall M, Munyombwe T, et al. A nationwide causal mediation analysis of survival following ST-elevation myocardial infarction. *Heart*. 2020;106:765-771.

9. Ohm J, Kuja-Halkola R, Warnqvist A, et al. Socioeconomic disparities and mediators for recurrent atherosclerotic cardiovascular disease events after a first myocardial infarction. *Circulation*. 2023;148:256-267.

10. Powell KL, Stephens SR, Stephens AS. Cardiovascular risk factor mediation of the effects of education and genetic risk score on cardiovascular disease: a prospective observational cohort study of the Framingham Heart Study. *BMJ Open*. 2021;11:e045210.

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