Review of Mediation Analysis

Fang Liu[1] and Jie Chen[2]
[1]Merck & Co., Inc.
[2]Overland Pharma

BIOP 2020 (Virtual)

Pr Proprietary

Why use mediation analysis?

- The utility of randomized controlled trials (RCTs) can be extended beyond the estimation of the effects of interventions on health outcomes.

- Clinicians and policy-makers may be interested in how the intervention works (or fails to work) through hypothesized causal mediation analysis by decomposing the treatment effect into **an indirect effect** mediated by a given intermediate variable and **the remaining direct effect**.

- After identifying the intermediate variable, researchers and clinicians can refine and adapt interventions to improve the effectiveness of health interventions and guide implementation.

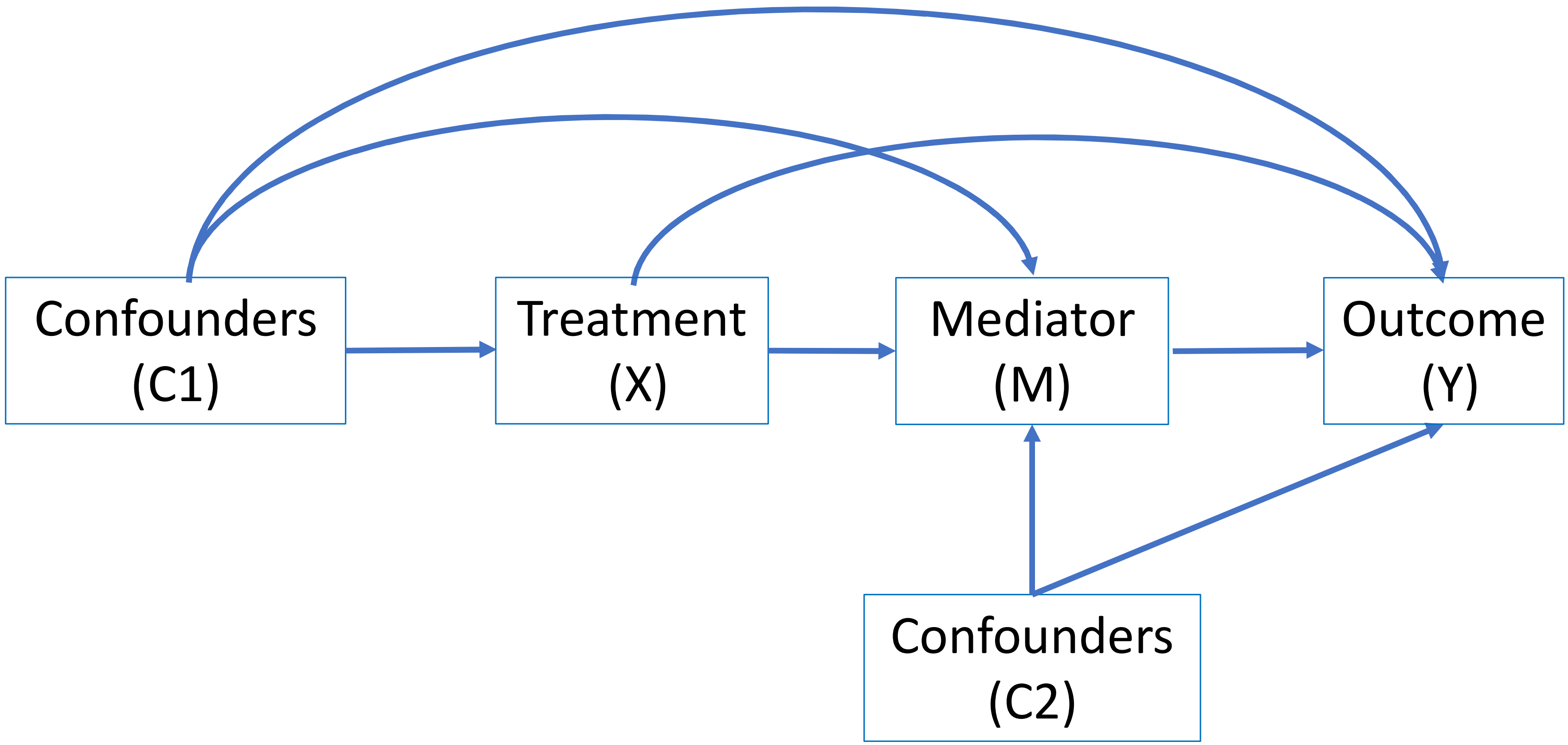
Example 1 (How did the intervention work?)

- The Strengthening And stretching for Rheumatoid Arthritis of the Hand Trial (SARAH) trial (n = 490) showed that an **exercise program (X=1)** for people with rheumatoid arthritis improved **hand function (Y)** more than **usual care (X=0) : total effect** = 4.4 [95% confidence interval (CI), 1.5–7.2] (Lee et. al (2019))
- After the trial was completed, **causal mediation analysis** was used to determine how much of the intervention effect was mediated by increases in **grip strength (M)**.
- A causal mediation analysis of complete cases (n = 387) indicated that 25% of the intervention effect on hand function at 12 months was mediated by increases in grip strength at 4 months (**Indirect Effect** = 1.1 [0.3,2.1]).
  - This indicates that exercise improves hand function partly by increasing hand strength.
- The analysis also suggests that a substantial proportion of the total intervention effect is mediated through other pathways (**Direct Effect**=3.3 [0.5,6.3]).
  - Future research might seek to identify these alterative mechanisms with the aim of further refining the intervention

Example 2 (Why didn't the intervention work?)

- The EXercise or Advice after ankle fracture (EXACT) trial (n = 214) didn't find evidence that a **rehabilitation program with advice (X=1)** was effective at **improving lower-limb function (Y)** than **advice alone (X=0)** for patients with ankle fracture**: total effect** = − 0.5 [− 5.0, 3.8] (Lee et. al (2019)).
- A hypothesized mechanism was that rehabilitation would increase **physical activity levels (M)**, which in turn would improve the lower-limb function. However, a causal mediation analysis found no evidence that physical activity at 1 month influenced function at 3 months (**indirect effect**=-0.4 [-2.1, 1.0])
- The analysis suggested that a change from low to high **physical activity** would improve lower-limb function by 8.7 points [2.2, 15.3]. However, the rehabilitation program failed to increase physical activity (ratio of odds of being classified as low physical activity = 0.9 [0.6, 1.2]).
- It might be possible to produce functional gains if physical activity levels could be increased using other interventions, which may guide the development of new interventions in this population.

Causal Diagram for Mediation Analysis



Proprietary

Traditional Approaches to Mediation Analysis (Baron and Kenny, 1986)

- Difference Method

$$E[Y|x,c] = \phi_0 + \phi_1 x + \phi_4' c$$
$$E[Y|x,m,c] = \theta_0 + \theta_1 x + \theta_2 m + \theta_4' c$$
$$DE = \theta_1$$
$$IE = \phi_1 - \theta_1$$

- Product Method

Outcome model: $E[Y|x,m,c] = \theta_0 + \theta_1 x + \theta_2 m + \theta_4' c$

Mediator model: $E[m|x,c] = \beta_0 + \beta_1 x + \beta_4' c$

$$DE = \theta_1$$
$$IE = \beta_1 \theta_2$$

- The two methods coincide for a continuous outcome and mediator with linear regression models fit by ordinary least square, but not for logistic regression models.
- The traditional approaches have important limitations concerning models with interactions or nonlinearities.
- c: Confounding variables; IE: indirect effect; DE: different effect;

Counterfactual-based Mediation analysis

- Let $Y_i(x)$ be the counterfactual outcome for subject i, when i has been assigned to treatment x.
- For a binary treatment ($x = 0$ or $x = 1$),
  - Individual level causal effect: $Y_i(1) - Y_i(0)$
  - Population average total causal effect: $E(Y(1) - Y(0))$
- Let $Y(x, M(x))$ denotes the potential outcome that would have been observed under treatment level x and mediator value m.
- Under the composition assumption, $\mathrm{Y}(x, M(x)) = \mathrm{Y}(x)$
- Natural (pure) direct effect (NDE) express the expected treatment -induced change in outcome when keeping the mediator fixed at the value that had naturally have been observed if untreated ($x = x^*$).

$$NDE(x^*) = E\{Y\big(x, M(x^*)\big) - Y(x^*, M(x^*))\}$$

- Natural indirect effect: $NIE(x) = E\big\{Y\big(x, M(x)\big) - Y\big(x, M(x^*)\big)\big\}$
- Average total effect: $Y(x) - Y(x^*)$= $NDE + NIE$

Proprietary

Assumptions to ensure identifiability of natural direct and indirect effects

- **No uncontrolled confounding**: assume variables collected in C are sufficient for controlling confounding for
  - Treatment-outcome relationship: hold in randomized trials
  - Treatment-mediator relationship: hold in randomized trials
  - Mediator-outcome relationship:
- **No mediator-outcome confounder** that is affected by the treatment (no arrow from X to C2)

- Sensitivity analysis should be provided for possible violations of the identification assumptions

Mediation Formula (Pearl et. al, 2012)

- Under the four assumptions,

$$E\{Y(\mathrm{x}, M(\mathrm{x}))|C\} = \sum_m E(Y|X = x, M = m, C)\mathrm{Pr}(M = m|X = x^*, C)$$

- Based on the above mediation formula, natural direct and indirect effects can be obtained through a combination of parameter estimates from a regression model for the outcome and a regression model of the mediator, even when there are interactions and non-linearities.
- When both outcome Y and mediator M obey linear model, the mediation formula is in line with the traditional approach.
- Available software to implement mediation analysis: SPSS/SAS macros developed (Valeri & Vanderweele, 2013); R package MEDIATION; etc.

Limitations of Mediation analysis using Mediation Formula

- The way to compute the natural direct and indirect effects differ substantially between different types of mediator or outcome.
- It could be very complicate depending on the models, especially when estimating the standard error.
- Even simple models for the mediator and outcome (e.g., logistic models for both mediator and outcome) tend to produce complex expressions of natural indirect and direct effects, which could make results difficult to report.

$$logit(P(Y = 1|x, m, c) = \theta_0 + \theta_1 x + \theta_2 m + \theta_4' c$$
$$logit(P(M = 1|x, c) = \beta_0 + \beta_1 x + \beta_4' c$$

$$Pr\{Y(\mathrm{x}, M(x^*)) = 1 | C\} = expit(\theta_0 + \theta_1 x + \theta_2 + \theta_4' c) expit(\beta_0 + \beta_1 x^* + \beta_4' c) + expit(\theta_0 + \theta_1 x + \theta_4' c)\{1 - expit(\beta_0 + \beta_1 x^* + \beta_4' c)\}$$

The natural direct and indirect effect odds ratio estimates will vary with different covariate levels and treatment, make the hypothesis testing of the natural direct and indirect effect infeasible.

Proprietary

Natural Effect Model (Lange, 2012)

Natural Effect Model includes both natural direct and indirect effects in one model:

$$\text{g}[E\{Y(x, M(x^*))|C\}] = \beta' W(x, x^*, C)$$

where $g(.)$ is a known canonical link function and $W(x, x^*, C)$ is a know vector with components that may depend on x, x^*, and C. For example:

$$\text{g}[E\{Y(x, M(x^*))|C\}] = \beta_0 + \beta_1 x + \beta_2 x^* + \beta_3 C$$

When g is the identity link function,

- $\beta_1(x - x^*)$ capture the natural direct effect $E\{Y\big(x, M(x^*)\big) - Y(x^*, M(x^*))\}$;
- $\beta_2(x - x^*)$ capture the natural indirect effect $E\{Y\big(x, M(x)\big) - Y(x, M(x^*))\}$.

When g is the logit link,

- $\exp(\beta_1(x - x^*))$ captures natural direct effect odds ratio
- $\exp(\beta_2(x - x^*))$ captures natural indirect effect odds ratio

Advantage of Natural Effect Model

- More flexible, it can handle a larger class of parametric models for the mediator and outcome.
- Estimates can be expressed on more natural effect scales (i.e., a scale that corresponds to the link-function of the outcome model), avoiding the potential induced dependence on exposure or covariate levels.
- Hypothesis testing is simplifed.

Natural Effect Model Implementation

- $Y(x, M(x^*))$ is only observable when $x^* = x$ (obersved treatment). When x^* differs x, $Y(x, M(x^*))$ is missing. Data needs to be expanded to include $Y(x, M(x^*))$ when $x^* = x$ and $x^* \neq x$.
  - Weighting-based approach
  - Imputation-based approach
- More imputation strategies and comparioson (Vansteelandt 2012)
- Implemented with R package: Medflex
- R package Medflex does not offer any tools for assessing the sensitivity for possible violations of the identification assumptions of the causal estimands.

Proprietary

Summary

- Mediation analysis can disentangle the indirect or mediated effect of a treatment on an outcome through given intermediaries, from the remaining direct effect.
  - Mediation formula: could be very complicate.
  - Natural effect model: very flexible and easy to implement. However, the R package Medflex does not offer sensitivity analysis.

Reference

- Baron R and Kenny D. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology.* 1986; 51(6), 1173–1182.
- Lee H, Herbert RD, Lamb SE, Moseley MA, McAuley HJ. Investigating causal mechanisms in randomised controlled trials. *Trials.* 2019; 20:524.
- Lange T, Vansteelandt S, Bekaert M. A simple unified approach for estimating natural direct and indirect effects. *Am J Epidemiol.* 2012;176:190-195.
- Pearl J. The Causal Mediation Formula – A Guide to the Assessment of Pathways and Mechanisms. *Prevention Science*. 2012; 13:426–436.
- Theis L, Kim WH, Rikke S and Soren G. A comparison of 5 software implementations of mediation analysis. *Epidemiol Health*. 2017; 39.
- Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods*. 2013;18:137-150.
- Vansteelandt S, Bekaert M, Lange T. Imputation strategies for the estimation of natural direct and indirect effects. *Epidemiol Methods.* 2012;1:131-158

Fang.liu11@merck.com

Back up

Proprietary

Natural effect model implement (Weighting-based approach)

- Estimate a suitable model for the exposure conditional on confounders by using the original dataset.
- Estimate a suitable model for the mediator conditional on treatment and baseline variables by using the original dataset.
- Construct a new dataset by repeating each observation in the original dataset twice and including an additional variable x^*, which is equal to the original exposure for the first replication and equal to the opposite of the actual exposure for the second replication.
- Compute weighs by apply the fitted models from steps1 and 2 to the new dataset.
- Fit a suitable model to the outcome including only x and x^* (and perhaps their interaction) as covariates and weighted by the weights from the previous step.