Causal Moderated Mediation Analysis

A Causal Investigation of Heterogeneity in Mediation Mechanisms: Methods and Software

Xu Qin

University of Pittsburgh

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Outline

- Background of mediation analysis and moderated mediation analysis
- Potential outcomes framework
- Causal mediation analysis and causal moderated mediation analysis
  - Definition
  - Identification
  - Estimation
- Sensitivity analysis for causal moderated mediation analysis
- R package implementation

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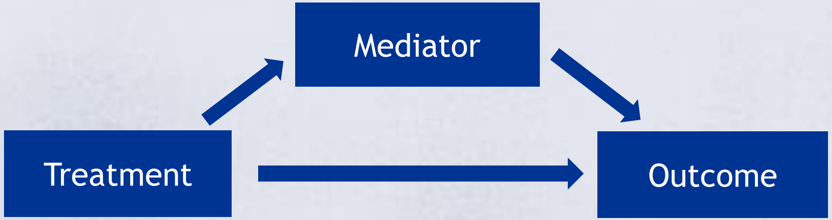
Background of Mediation Analysis

What Is mediation?

- **Mediation** uncovers the black box underlying the impact of a treatment on an outcome. It helps understand the mechanisms, pathways, and intermediates whereby a treatment affects an outcome and thus answers the question of WHY and HOW.
- A **mediator** represents the generative mechanism through which the treatment is able to influence the outcome (Baron and Kenny, 1986).
- **Mediation analysis** decomposes the total treatment effect into
  - an indirect effect transmitted through the hypothesized mediator;
  - a direct effect representing the contribution of other unspecified pathways.



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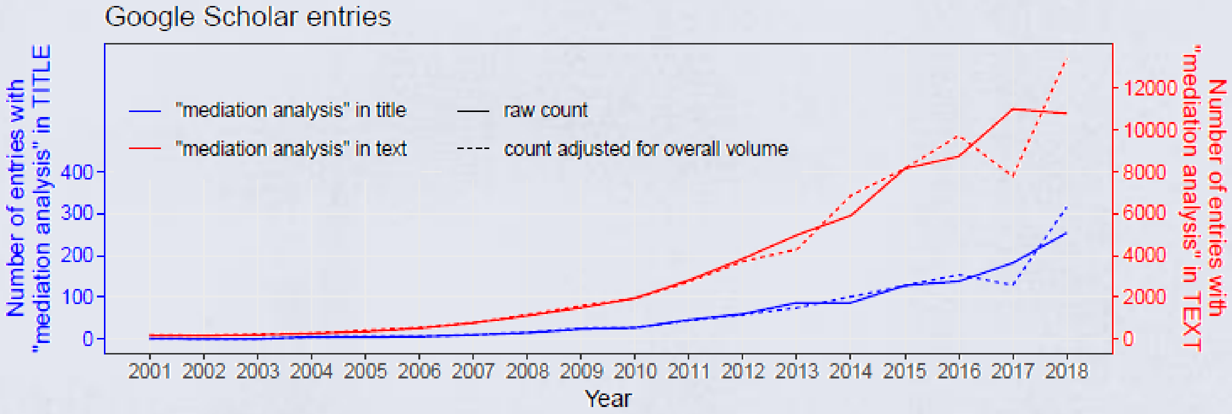
Increasing trend in the popularity of mediation analysis

- The number of entries in Google Scholar that have “mediation analysis” in the title or text have been growing exponentially.



- Mediation analysis is now encountered, or even required, by some research funding agencies, such as the National Institute of Mental Health.

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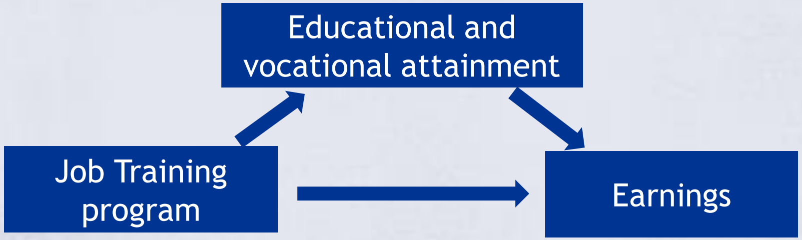
Nguyen et al. (2021)

Why is mediation analysis of interest?

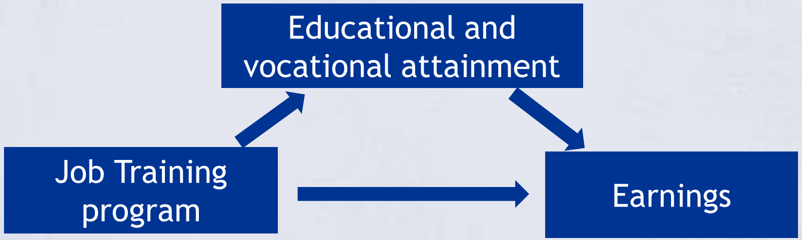
- For explanation and understanding
  - E.g., how did a job training program improve earnings?
  - Did it improve participants' educational and vocational attainment, which subsequently increased earnings?
  - How much was the total impact of the program on earnings transmitted through other pathways?



VanderWeele (2015) pp.11

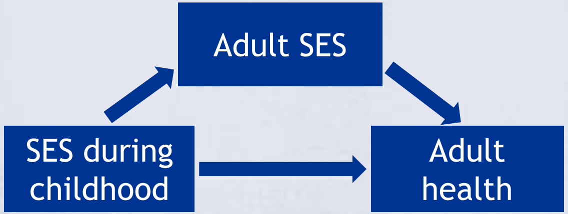
Quiz 1

- What is the mediator in this example?
  A. Job training program
  B. Educational and vocational attainment
  C. Earnings



Why is mediation analysis of interest?

- Help confirm and refute theory
  - E.g., there remains debate as to whether the association between childhood SES and health outcome is because
    - low SES during childhood affects adult SES, which in turn affects adult health (a "social trajectory" model),
    - or whether childhood SES affects adult health through pathways other than adult SES (a "latent effects/sensitive period" model).



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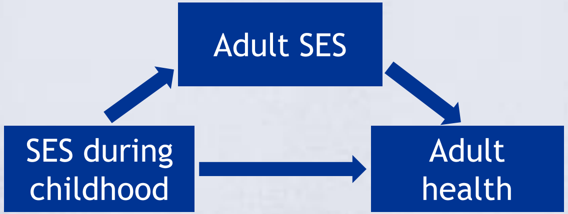
VanderWeele (2015) pp.11

Quiz 2

- In this example, mediation analysis decomposes
  - A. The effect of SES during childhood on adult SES
  - B. The effect of SES during childhood on adult health
  - C. The effect of adult SES on adult health



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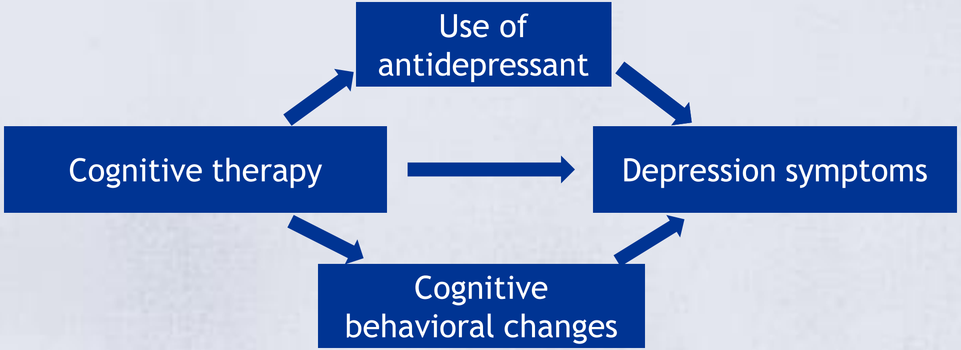
Why is mediation analysis of interest?

- Refine an intervention by improving components of the intervention that transmit a large portion of the treatment impact or discarding components that are not important.
  - E.g., a cognitive therapy intervention was found to have a beneficial effect on depression symptoms.
  - If the intervention were beneficial only because of **higher use of antidepressant** but not because of **cognitive behavioral changes**, then the cognitive behavioral aspects of the intervention could perhaps be abandoned without much loss and a more cost-effective intervention just focusing on antidepressant adherence could be developed.



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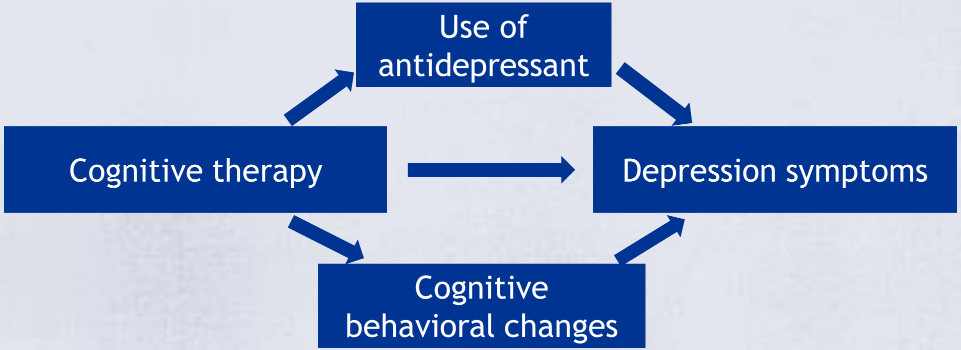
VanderWeele (2015) pp.12

Quiz 3

- In this example, the total effect of cognitive therapy on depression symptoms is decomposed into which of the following components? (Choose more than one items)
  A. The indirect effect transmitted through use of antidepressant
  B. The indirect effect transmitted through cognitive behavioral changes
  C. The direct effect transmitted through all the other pathways
  D. The effect of cognitive therapy on antidepressant
  E. The effect of cognitive behavioral changes on depression symptoms



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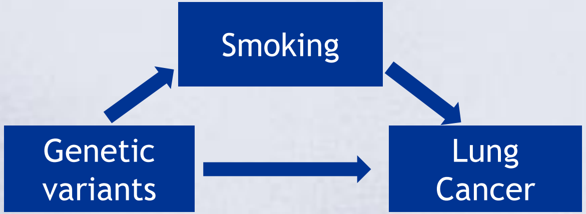
Why is mediation analysis of interest?

- Understand why an intervention is found to have a null or negative effect on an outcome.
  - It is possible that an intervention might affect the outcome positively through one mechanism and negatively through a different mechanism. Such knowledge may be useful in determining whether an intervention needs to be refined by better targeting a particular mechanism.
- We may not be able to intervene on the exposure but may eliminate a detrimental effect of an exposure by intervening instead on some particular mechanism.
  - E.g., we cannot intervene directly on the genetic variants, but we might be interested in how much of the effect of the genetic variants on lung cancer we could block if we could intervene to eliminate smoking.



VanderWeele (2015) pp.13

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Example -- NEWWS

- National Evaluation of Welfare-to-Work Strategies (NEWWS) study
- The study randomly assigned 694 participants, who were mostly low-income single mothers with young children.
    - Labor Force Attachment (LFA) program (208) aimed at moving low-income parents from welfare to work by providing employment-focused incentives and services.
    - Control group (486) received aid from the Aid to Families with Dependent Children (AFDC) program without requirement for working.
- Mediator: If one was ever employed during the two-year period after randomization
- Outcome: Maternal depression at the end of the second year after randomization.

Example

- Hypothesized mediation mechanism: attending the LFA program would increase an individual's chance of being employed, which would subsequently decrease his or her depression level. In other words, employment mediates the effect of LFA on depression.

- The total effect of LFA on depression can be decomposed into
  - indirect effect: the change in depression attributable to the LFA-induced change in employment rate.
  - direct effect: the impact of LFA on depression without changing employment rate.

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Traditional mediation analysis methods

- Path analysis model (Baron & Kenny, 1986)

$$M = \beta_0^m + \beta_t^m T + \varepsilon_M$$
$$Y = \beta_0^y + \beta_t^y T + \beta_m^y M + \varepsilon_Y$$

- Indirect effect: $\beta_t^m \beta_m^y$
- Direct effect: β_t^y

Limitations of the traditional SEM/path analysis

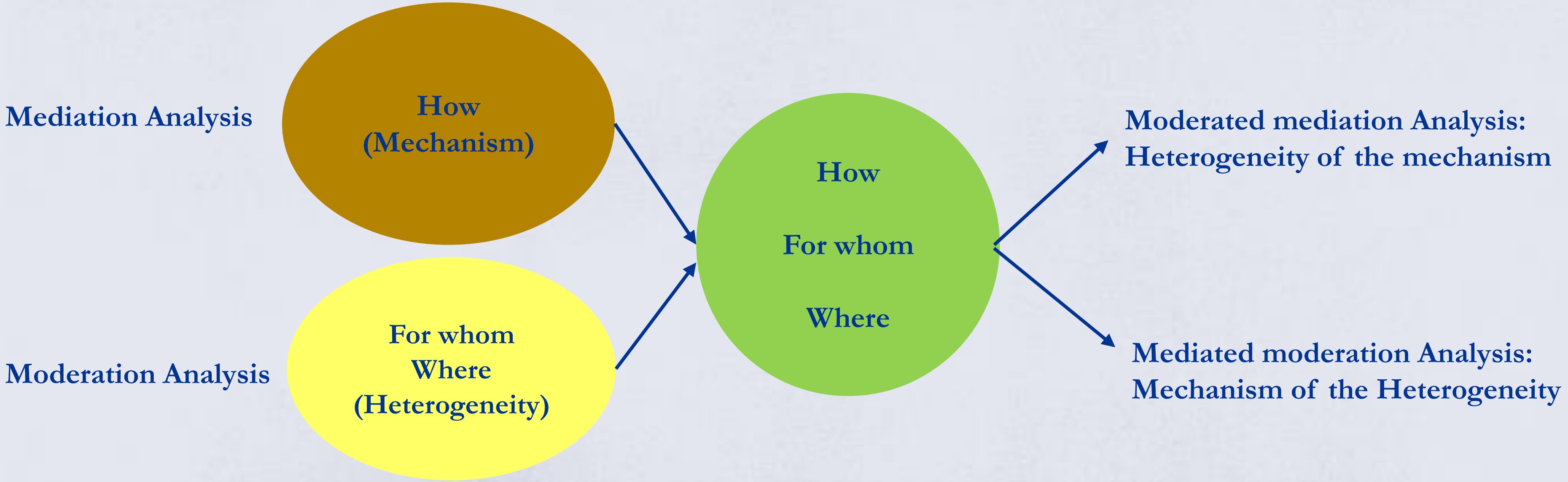
- They do not carefully account for confounders.
  - Omitting confounders of the treatment-mediator, treatment-outcome, and mediator-outcome relationships from the analysis would result in biased indirect and direct effect estimates.
  - Even if the treatment is randomized, mediator values are typically generated through a natural process rather than being experimentally manipulated. As a result, individuals displaying different mediator values tend to differ systematically in many aspects that would confound the relationship between the mediator and the outcome, i.e., affect both the mediator and the outcome.
  - E.g., participants who were less willing to accept a low-wage job before participating in the study might be less likely to be employed (mediator) and suffer from more severe depression (outcome) if assigned to LFA.

Limitations of the traditional SEM/path analysis

- They ignore the common treatment-by-mediator interaction
  - Treatment effect may be generated not only by changing the mediator but also by changing the relationship between the mediator and the outcome (Judd & Kenny, 1981).
  - E.g., employment (mediator) may be more beneficial to psychological well-being (outcome) under the LFA condition than under the control condition.

Background of Moderated Mediation Analysis

Mediation and moderation analysis



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Quiz 4

- Which type of analysis can answer this research question: does the Head Start program improve children's vocabulary score through parent reading?
    A. Mediation analysis
    B. Moderation analysis
    C. Moderated mediation analysis

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Quiz 5

- Which type of analysis can answer this research question: is the Head Start program more effective among boys than among girls?
    A. Mediation analysis
    B. Moderation analysis
    C. Moderated mediation analysis

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Quiz 6

- Which type of analysis can answer this research question: does parent reading play a more important mediating role underlying the Head Start impact on vocabulary score among parents with higher education than among those with lower education?
    A. Mediation analysis
    B. Moderation analysis
    C. Moderated mediation analysis

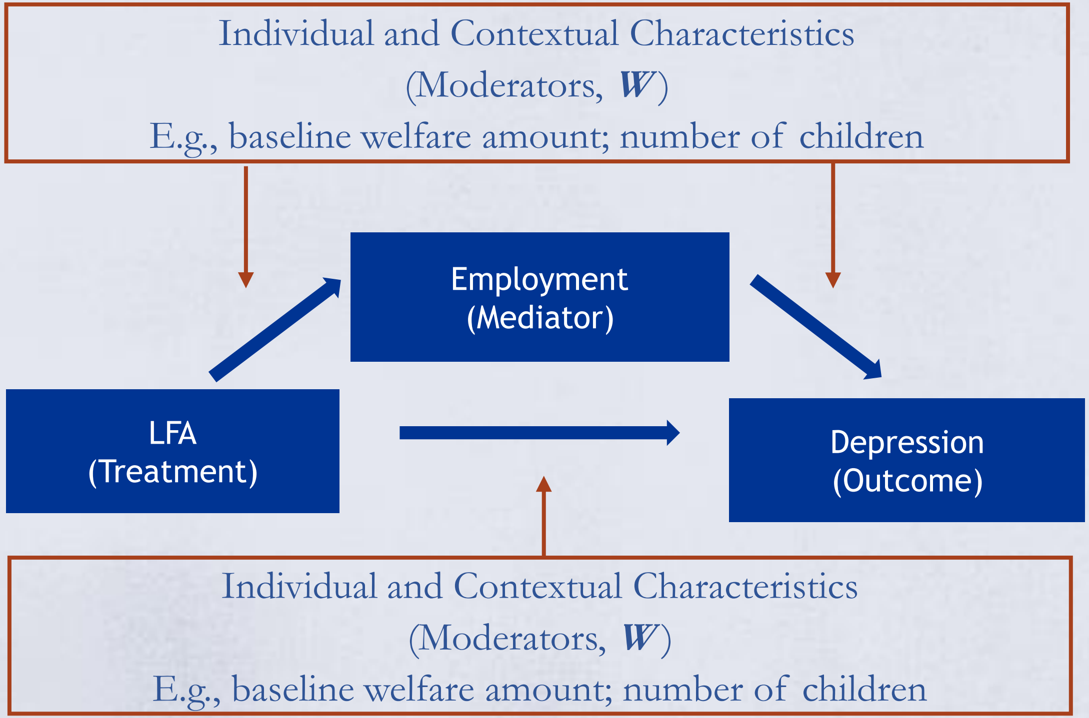
Why is moderated mediation analysis of interest?

- The importance of investigating the heterogeneity of the impact of an intervention has become increasingly valued.
- Important research questions include whether the intervention impact is generalizable across individuals and contexts, for whom and under what contexts the intervention is effective, and why.
- To answer such questions, it is necessary to unpack the underlying mediation mechanism and assess how it is moderated by individual and contextual characteristics.
- It may reveal a need to refine the intervention theory and may suggest ways to improve a program by tailoring the program components to different individuals under different contexts.

Pretreatment moderator

- An explicit moderator defines subpopulations between which the mediation mechanisms may differ.
- Muller et al. (2005) emphasized the pretreatment nature of the moderator and described it as a measure of some stable individual or contextual differences that are assumed not to be affected by the treatment yet are related to different mediation mechanisms.
- Note: While this course is focused on a pretreatment moderator, a moderator does not have to be pretreatment.
  - If a moderator is concurrent with the mediator, the estimation and inference stay the same, while the definitions and identification assumptions change.
  - If a moderator is also a sequential mediator, we need to conduct a mediation analysis for sequential mediators that interact with each other (Daniel et al., 2015).

Hypothesized moderated mediation mechanism



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Other examples

- National Study of Learning Mindset
  - Treatment: Growth mindset intervention vs. control
  - Mediator: Challenge-seeking behaviors
  - Outcome: Math achievement
  - Moderator: School achievement level
- Head Start Impact Study
  - Treatment: Head Start vs. control
  - Mediator: Parent reading to child
  - Outcome: Vocabulary score
  - Moderator: Parent education

Traditional moderated mediation analysis methods

- Target parameter: conditional indirect effect given values of moderators $\boldsymbol{W}$
- Estimate the conditional indirect effect by extending path analysis

$$M = \beta_0^m + \beta_t^m T + \varepsilon_M$$
$$Y = \beta_0^y + \beta_t^y T + \beta_m^y M + \varepsilon_Y$$

  - Fit separate models and estimate $\beta_t^m \beta_m^y$ within levels of $\boldsymbol{W}$.
  - Incorporate $\boldsymbol{W}$ and their interactions with T and/or M in the model and define the conditional indirect effect as a function of $\boldsymbol{W}$ under different scenarios.
- Test moderated mediation by assessing if the indirect effect significantly varies by $\boldsymbol{W}$
  - Test the significance of the interaction of $\boldsymbol{W}$ with path $T \rightarrow M$ (β_t^m) or path $M \rightarrow Y$ (β_m^y). **Not Equivalent**
  - Hayes index **Apply only if indirect effect is a linear function of *W***
  - Test the difference in the indirect effect between two given sets of values of $\boldsymbol{W}$

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Limitations of the traditional methods

- Pay less attention to the influence of confounders.
  - Ignoring confounders of the treatment-mediator, treatment-outcome, or mediator-outcome relationship would generate biased results, and failure to assess the influence of unmeasured confounders may result in misleading conclusions.
- No general definition of the conditional indirect effect is available beyond specific mediator and outcome models.
  - The conditional indirect effect is defined differently under different scenarios (e.g., only β_t^m or β_m^y is moderated; both β_t^m and β_m^y are moderated; β_t^m is moderated by one moderator while β_m^y is moderated by another).
- When either the mediator or the outcome is binary, or when the mediator or outcome model is nonlinear, moderated mediation analysis has not been developed under the traditional framework, to the best of our knowledge.

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5-Minute Break
Q&A

Potential Outcomes Framework

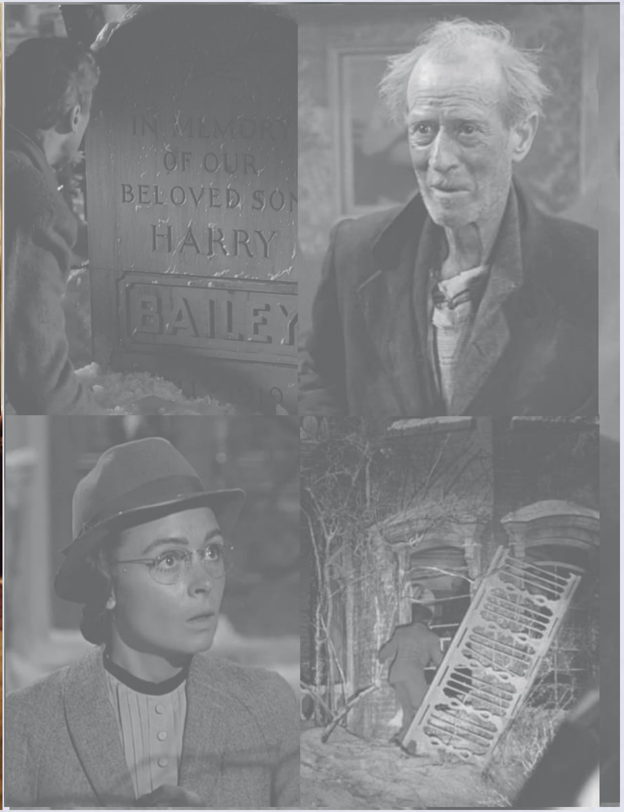
Potential outcomes framework

- Under the potential outcomes framework, every individual has a potential outcome corresponding to each level of the intervention, manipulation, or treatment.
- It is called "potential" because only one outcome is observed, depending on which level the individual is assigned to, while the outcomes under the other levels are unobservable.

Movie: It’s a Wonderful Life (1946)

Observed

Counterfactual (Unobservable)



Causal effect: a comparison of potential outcomes for the same unit.

Causal Mediation Analysis

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Potential mediator and potential outcome

- For each individual i,
- $M_i(1)$: potential employment status (mediator) if assigned to LFA ($\mathrm{T} = 1$).
- $M_i(0)$: potential employment status (mediator) if assigned to the control group ($\mathrm{T} = 0$).
- $Y_i(1) \equiv Y_i(1, M_i(1))$: potential depression level (outcome) if assigned to LFA ($\mathrm{T} = 1$).
- $Y_i(0) \equiv Y_i(0, M_i(0))$: potential depression level (outcome) if assigned to the control group ($\mathrm{T} = 0$).
- $Y_i(1, M_i(0))$: potential depression level (outcome) if assigned to LFA ($\mathrm{T} = 1$), while the potential employment status (mediator) takes the value under the counterfactual control condition ($\mathrm{T} = 0$).
- $Y_i(0, M_i(1))$: potential depression level (outcome) if assigned to the control group ($\mathrm{T} = 0$), while the potential employment status (mediator) takes the value under the counterfactual LFA condition ($\mathrm{T} = 1$).

Quiz 7

- Which of the following is the right notation of the potential depression level (outcome) if an individual i were assigned to LFA ($\mathrm{T} = 1$)?
   A. $Y_i(1, M_i(0))$
   B. $Y_i(1, M_i(1))$
   C. $Y_i(0, M_i(0))$
   D. $Y_i(0, M_i(1))$

Quiz 8

- Which of the following is the right notation of the potential depression level (outcome) if an individual i were assigned to LFA ($T = 1$), while the potential employment status (mediator) takes the value under the counterfactual control condition ($T = 0$)?
  A. $Y_i(1, M_i(0))$
  B. $Y_i(1, M_i(1))$
  C. $Y_i(0, M_i(0))$
  D. $Y_i(0, M_i(1))$

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SUTVA

- The potential outcomes are defined under SUTVA.
  - No interference
    - An individual's potential mediators do not depend on other individuals' treatment status
      - E.g., this assumption would be violated if an individual had higher chance of being employed when both the individual and his/her best friend were assigned to LFA than when the individual was assigned to LFA, but his/her friend was assigned to the control group.
    - An individual's potential outcomes do not depend on other individuals' treatment status or mediator values
      - E.g., this assumption would be violated if an individual's depression level depends on his/her best friend's treatment assignment or chance of being employed.

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SUTVA

- The potential outcomes are defined under SUTVA.
  - No hidden variations of treatments
    - There is only one version of each treatment level.
    - E.g., this assumption would be violated if LFA program has different versions of implementation.

Definitions of individual effects

	$T_i = 1$	$T_i = 0$
$M_i(1)$	$\boldsymbol{Y_i(1, M_i(1))}$	
$M_i(0)$	$\boldsymbol{Y_i(1, M_i(0))}$	$Y_i(0, M_i(0))$

$$\boldsymbol{Y_i(1, M_i(1)) - Y_i(1, M_i(0))}$$

Natural indirect effect (Pearl, 2001)
Total indirect effect (Robins and Greenland,1992)

Definitions of individual effects

	$T_i = 1$	$T_i = 0$
$M_i(1)$	$Y_i(1, M_i(1))$	
$M_i(0)$	$\boldsymbol{Y_i(1, M_i(0))}$	$\boldsymbol{Y_i(0, M_i(0))}$

$$\boldsymbol{Y_i(1, M_i(0)) - Y_i(0, M_i(0))}$$

Natural direct effect (Pearl, 2001)
Pure direct effect (Robins and Greenland,1992)

Definitions of individual effects

Employment (Mediator: M)

LFA (Treatment: T)

Depression (Outcome: Y)

	$T_i = 1$	$T_i = 0$
$M_i(1)$	$Y_i(1, M_i(1))$	$Y_i(\mathbf{0}, M_i(\mathbf{1}))$
$M_i(0)$		$Y_i(\mathbf{0}, M_i(\mathbf{0}))$

$\boldsymbol{Y_i(0, M_i(1)) - Y_i(0, M_i(0))}$

Pure indirect effect (Robins and Greenland,1992)

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Definitions of individual effects

	$T_i = 1$	$T_i = 0$
$M_i(1)$	$\boldsymbol{Y_i(1, M_i(1))}$	$\boldsymbol{Y_i(0, M_i(1))}$
$M_i(0)$		$Y_i(0, M_i(0))$

$$\boldsymbol{Y_i(1, M_i(1)) - Y_i(0, M_i(1))}$$

Total direct effect (Robins and Greenland,1992)

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Quiz 9

- Which of the following effects denote an indirect effect? (Choose more than one items)
  A. $Y_i(1, M_i(1)) - Y_i(1, M_i(0))$
  B. $Y_i(1, M_i(0)) - Y_i(0, M_i(0))$
  C. $Y_i(0, M_i(1)) - Y_i(0, M_i(0))$
  D. $Y_i(1, M_i(1)) - Y_i(0, M_i(1))$

Definitions of individual effects

- Two different two-way decompositions of the total effect (TE)
  - Decomposition I (more commonly used)

$$
\begin{array}{ccc}
 & Y_i(1, M_i(1)) - Y_i(0, M_i(0)) & \\
\swarrow & & \searrow \\
Y_i(1, M_i(1)) - Y_i(1, M_i(0)) & & Y_i(1, M_i(0)) - Y_i(0, M_i(0)) \\
\text{NIE (TIE)} & & \text{NDE (PDE)}
\end{array}
$$

  - Decomposition II

$$
\begin{array}{ccc}
 & Y_i(1, M_i(1)) - Y_i(0, M_i(0)) & \\
\swarrow & & \searrow \\
Y_i(0, M_i(1)) - Y_i(0, M_i(0)) & & Y_i(1, M_i(1)) - Y_i(0, M_i(1)) \\
\text{PIE} & & \text{TDE}
\end{array}
$$

  - The two decompositions are not equivalent in the presence of treatment-by-mediator interaction.
  - Natural treatment-by-mediator interaction effect INT = TIE – PIE = TDE - PDE
- Three-way decomposition: TE = PIE + PDE + INT

Definitions of population average effects

If a treatment has more than two categories or is continuous, we can 1 and 0 with any two different values of the treatment, t and t'. For a binary treatment, $t = 1$ and $t' = 0$.

	Notation	Definition
Total Treatment Effect	$TE = E[Y(t, M(t))] - E[Y(t', M(t'))]$	Overall average change in the potential outcome if the treatment condition is changed from t' to t
Natural Indirect Effect (Total Indirect Effect)	$NIE = E[Y(t, M(t))] - E[Y(t, M(t'))]$	Average change in the potential outcome if the treatment is fixed at condition t, while the potential mediator is changed from the level that would be observed under the treatment condition t' to that under t
Natural Direct Effect (Pure Direct Effect)	$NDE = E[Y(t, M(t'))] - E[Y(t', M(t'))]$	Average change in the potential outcome if the treatment condition is changed from t' to t, while the potential mediator is held at the level that would be observed under the treatment condition t'
Pure Indirect Effect	$PIE = E[Y(t', M(t))] - E[Y(t', M(t'))]$	Average change in the potential outcome if the treatment is fixed at condition t', while the potential mediator is changed from the level that would be observed under the treatment condition t' to that under t
Total Direct Effect	$TDE = E[Y(t, M(t))] - E[Y(t', M(t))]$	Average change in the potential outcome if the treatment condition is changed from t' to t, while the potential mediator is held at the level that would be observed under the treatment condition t
Natural Treatment-by-Mediator Interaction Effect	$INT = NIE - PIE = TDE - NDE$	Average difference in how the treatment-induced change in the potential mediator affects the potential outcome between the treatment conditions t and t'.

5-Minute Break
Q&A

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Identification

	Treatment	Potential Outcomes			
Individual	T_i	$Y_i(1, M_i(1))$	$Y_i(0, M_i(0))$	$Y_i(1, M_i(0))$	$Y_i(0, M_i(1))$
1	1	25	?	?	?
2	1	5	?	?	?
3	1	10	?	?	?
4	1	2	?	?	?
5	0	?	30	?	?
6	0	?	2	?	?
7	0	?	8	?	?
8	0	?	10	?	?
Population Average		$E[Y(1, M(1))]$	$E[Y(0, M(0))]$	$E[Y(1, M(0))]$	$E[Y(0, M(1))]$

Identification: Relating unobservable quantities to observed data

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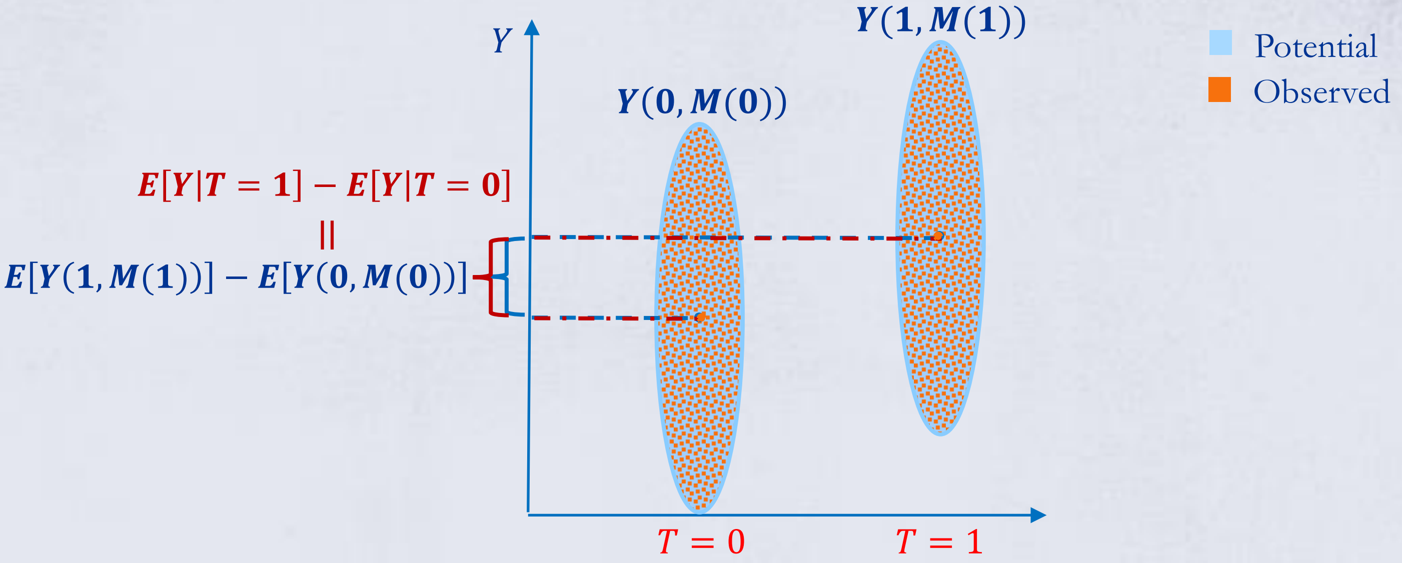
Identification of treatment effect



- The figure represents the ignorability assumption of treatment, which holds if treatment is randomized.

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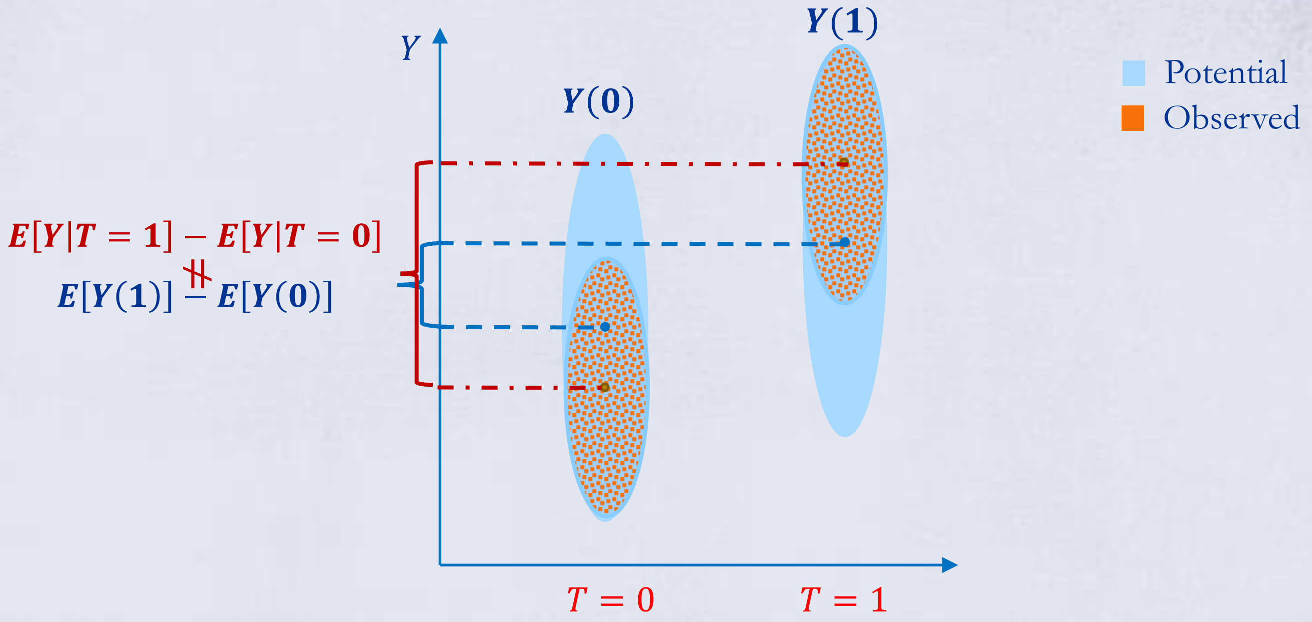
Identification of treatment effect



- The figure represents what would happen if treatment is not randomized, in which case the treatment effect can be identified under the strong ignorability of treatment:
  - **No unmeasured confounder of the T-Y relationship**, i.e., the treatment is as if randomized within levels of pretreatment covariates.
  - **Positivity assumption**, i.e., within levels of pretreatment covariates, every individual has a nonzero probability of receiving each treatment level.

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Identification assumption for causal mediation analysis

- Sequential Ignorability
  - **Strong ignorability of the treatment**
    - **No unmeasured confounder of the *T-M* or *T-Y* relationship**, i.e., the treatment is as if randomized within levels of pretreatment covariates.
    - **Positivity assumption**, i.e., within levels of pretreatment covariates, every individual has a nonzero probability of receiving each treatment level (positivity assumption).
  - **Strong ignorability of the mediator**
    - **No unmeasured pretreatment confounder and no posttreatment confounder of the *M-Y* relationship**, i.e., the mediator is as if randomized within the same treatment group or across treatment groups among individuals with the same levels of pretreatment covariates.
    - **Positivity assumption**, i.e., within levels of pretreatment covariates, every individual has a nonzero probability of taking each mediator value within the response space of the mediator under each treatment condition.

(Imai et al., 2010)

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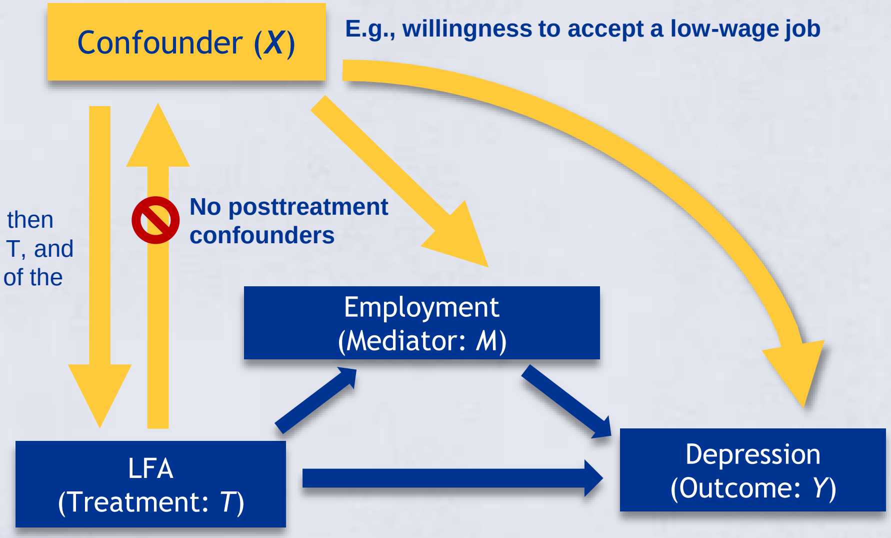
Identification assumption for causal mediation analysis

If treatment is randomized, then there is no arrow from X to T, and thus the strong ignorability of the treatment is guaranteed.



Quiz 10

- Which of the following confounds the relationship between the mediator and the outcome relationship?
  A. A covariate that affects both the treatment and the outcome.
  B. A covariate that affects both the treatment and the mediator.
  C. A covariate that affects both the mediator and the outcome.
  D. A covariate that affect the mediator only.

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Regression-based identification of mediation effects

- Path analysis models assume no treatment-by-mediator interaction TM and usually do not adjust for pretreatment covariates $\mathbf{X}$. VanderWeele and Vansteelandt (2009) relaxed these assumptions by further adjusting for TM and $\mathbf{X}$. For continuous mediator and outcome,

$$M = \beta_0^m + \beta_t^m T + \mathbf{X}\boldsymbol{\beta}_x^m + \varepsilon_m,$$

$$Y = \beta_0^y + \beta_t^y T + \beta_m^y M + \beta_{tm}^y TM + \mathbf{X}\boldsymbol{\beta}_x^y + \varepsilon_y.$$

- Under the sequential ignorability assumption and the above model-based assumptions, we can identify the population average of each potential outcome as

$$E[Y_i(t, M_i\,(t'))] = \beta_0^y + \beta_t^y t + \left(\beta_m^y + \beta_{tm}^y t\right)\left(\beta_0^m + \beta_t^m t' + E[\mathbf{X}]\boldsymbol{\beta}_x^m\right) + E[\mathbf{X}]\boldsymbol{\beta}_x^y$$

- Correspondingly,

$$NIE = \left(\beta_m^y + \beta_{tm}^y t\right)\beta_t^m (t - t'),$$

$$NDE = \left(\beta_t^y + \beta_{tm}^y\left(\beta_0^m + \beta_t^m t' + E[\mathbf{X}]\boldsymbol{\beta}_x^m\right)\right)(t - t').$$

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Causal Moderated Mediation Analysis

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Definition of the causal moderated mediation effects

- Averaging each individual-specific effect δ_i over individuals within given levels of the moderators $\boldsymbol{W}$, we define the conditional average of each effect (including the TE, TIE, PDE, PIE, and TDE) as

$$\delta_{\boldsymbol{w}} = E[\delta_i | \boldsymbol{W}_i = \boldsymbol{w}]$$

- Each moderated effect can be defined as a contrast of the conditional effect between subpopulations defined by two different levels of the moderators $\boldsymbol{W}$:

$$\delta_{MOD} = \delta_{\boldsymbol{w_1}} - \delta_{\boldsymbol{w_2}}$$

- These definitions intuitively formalize mediation and moderation without relying on any statistical models and apply to all the possible moderated mediation scenarios.

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Identification

- Assume that **within levels of moderators *W*,**
  - **Strong ignorability of the treatment**
    - No unmeasured confounder of the T-M or T-Y relationship.
    - Within levels of pretreatment covariates, every individual has a nonzero probability of receiving each treatment level.
  - **Strong ignorability of the mediator**
    - No unmeasured pretreatment confounder and no posttreatment confounder of the M-Y relationship.
    - Within levels of pretreatment covariates, every individual has a nonzero probability of taking each mediator value within the response space of the mediator under each treatment condition.

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Estimation

- Hierarchical form

$$M = \beta_0^m + \beta_t^m T + \mathbf{X}\boldsymbol{\beta}_x^m + \varepsilon_m, \varepsilon_m \sim N(0, \sigma_m^2)$$
$$Y = \beta_0^y + \beta_t^y T + \beta_m^y M + \beta_{tm}^y TM + \mathbf{X}\boldsymbol{\beta}_x^y + \varepsilon_y, \varepsilon_y \sim N\left(0, \sigma_y^2\right)$$

$$\beta_0^m = \beta_{00}^m + \beta_{0w}^m W$$
$$\beta_t^m = \beta_{t0}^m + \beta_{tw}^m W$$
$$\boldsymbol{\beta}_x^m = \boldsymbol{\beta}_{x0}^m + \boldsymbol{\beta}_{xw}^m W$$
$$\beta_0^y = \beta_{00}^y + \beta_{0w}^y W$$
$$\beta_t^y = \beta_{t0}^y + \beta_{tw}^y W$$
$$\beta_m^y = \beta_{m0}^y + \beta_{mw}^y W$$
$$\beta_{tm}^y = \beta_{tm0}^y + \beta_{tmw}^y W$$
$$\boldsymbol{\beta}_x^y = \boldsymbol{\beta}_{x0}^y + \boldsymbol{\beta}_{xw}^y W$$

Facilitates the specification and interpretation of moderation

- Combined form

$$M = \beta_{00}^m + \beta_{0w}^m W + \beta_{t0}^m T + \mathbf{X}\boldsymbol{\beta}_{x0}^m + \beta_{tw}^m WT + W\mathbf{X}\boldsymbol{\beta}_{xw}^m + \varepsilon_M$$
$$Y = \beta_{00}^y + \beta_{0w}^y W + \beta_{t0}^y T + \beta_{m0}^y M + \boldsymbol{\beta}_{x0}^y \mathbf{X} + \beta_{tw}^y WT + \beta_{mw}^y WM + W\mathbf{X}\boldsymbol{\beta}_{xw}^y + \beta_{tm0}^y TM + \beta_{tmw}^y WTM + \varepsilon_Y$$

- The models can be fitted with bootstrapping method, Monte Carlo method, or Bayesian method.

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(Qin & Wang, 2024)

Sensitivity Analysis

Why is sensitivity analysis essential?

- The identification strategies rely on the sequential ignorability assumption.
- The strong ignorability of the treatment is guaranteed by random treatment assignment.
- The strong ignorability of the mediator would be violated if there was an omitted pretreatment confounder or a posttreatment confounder of the mediator-outcome relationship.
    - E.g., among the participants with the same welfare amount and number of children prior to the randomization, those who were less willing to accept a low-wage job before participating in the study (pretreatment) or in the first year after participation (post-treatment) might be less likely to be employed in the two years after participation and tend to experience more depression at the end of the second year especially if assigned to the LFA program.
- A sensitivity analysis is necessary for determining
    - the influence of a potential omitted confounder; or
    - how strong omitted confounding needs to be for the sign or statistical significance of the original conclusions to be changed.

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Basic idea of sensitivity analysis

- If a confounder is observed but arbitrarily omitted from the analysis
  - Compare the results before and after including the omitted variables in the analysis
- If a confounder is unmeasured
  - Use **sensitivity parameters** to imply departures from the identification assumptions due to unmeasured confounding. In other words, the sensitivity parameters reflect the strength of unmeasured confounding.
  - Assess **point estimates** of the indirect and direct effects and their **standard errors** as functions of the sensitivity parameters.
  - The larger the magnitudes of the sensitivity parameters are for removing the effects or changing their significance, the **less sensitive** the results are.

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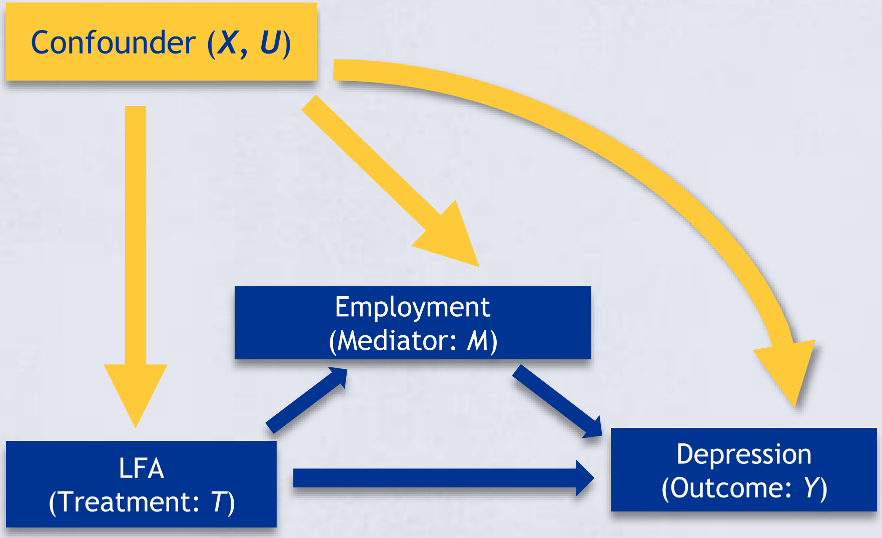
Note

- This section is focused on assessing the influence of unmeasured pretreatment confounding.
- A discussion on posttreatment confounding can be found on slides 103 and 110.
  - Reduce the possibility of posttreatment confounding by choosing the time point of measurement for the mediator to be relatively close to that for the treatment.
  - Adjust for posttreatment confounding
    - through a sensitivity analysis strategy
    - from an interventional perspective

Basic idea of the simulation-based sensitivity analysis method

- The goal of this study is to understand what the estimates of NIE and NDE and their standard errors would have been had we adjusted for an unmeasured pretreatment confounder U.
- To reach this goal, we derive a conditional distribution of U based on our assumptions about its prior distribution and its relationship with the outcome and the mediator.
- Given random draws of U from its conditional distribution, we are able to estimate NIE and NDE after the adjustment for U.



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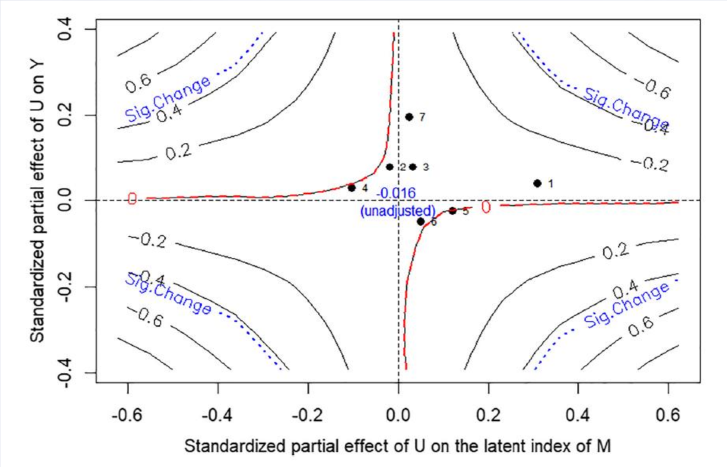
Simulation-based sensitivity analysis in R



Sensitivity analysis plot for PIE

- The x axis and y axis are the sensitivity parameters, which are the slopes of unmeasured confounder in the standardized mediator and outcome models.
- Each black contour represents the combinations of sensitivity parameters that lead to the same effect estimate as indicated by the number on the contour.
- The sensitivity parameters along the red dashed curves reduce the estimate to zero.
- Each blue dotted curve corresponds to the boundary at which the significance of the effect is changed at the significance level of .05. The effect is insignificant on the side that contains the zero line.
- The larger the magnitudes of the sensitivity parameters are for removing the effects or changing their significance, the less sensitive the results are.

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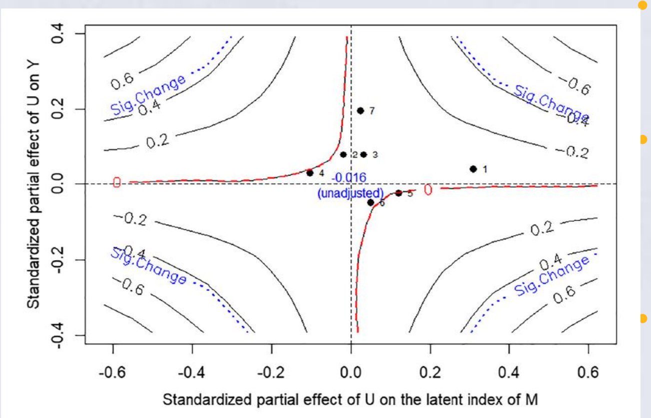
Simulation-based sensitivity analysis in R



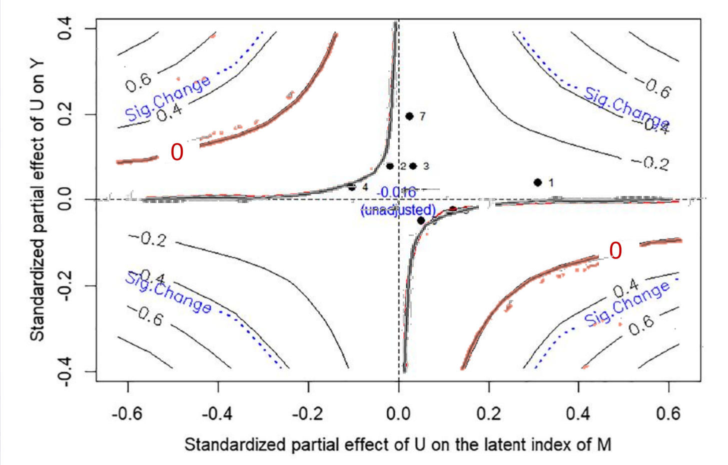
Sensitivity analysis plot for PIE

1-7 are respectively comparable to emp_prior, nevmar, hispanic, nohsdip, workpref, attitude, and depress_prior.

- Each dot corresponds to the conditional associations of each observed covariate with Y and M, which are used to calibrate the strength of the sensitivity parameters.
- The plot shows that, an additional adjustment of an unmeasured pretreatment confounder U would reverse the sign of PIE as long as the confounding role of U is as strong as one's baseline educational attainment (nohsdip) or work preference (workpref).
- Nevertheless, for the significance of PIE to be altered, U must be much stronger than the strongest observed pretreatment confounder. Because we have controlled for the most important pretreatment confounders in theory, it is almost impossible for the remaining confounders to reverse the significance of PIE even collectively.
- Hence, the sign of PIE may be sensitive, but its significance is more robust.
- Similarly, should there be a set of potential unmeasured pretreatment confounders, one could evaluate their collective influence by comparing their joint confounding role to the observed covariates.

Simulation-based sensitivity analysis in R

- The further away the red and blue contours are from the black dots, the less sensitive the results are to potential unmeasured pretreatment confounding.



5-Minute Break
Q&A

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R Implementation

R package `moderate.mediation`

- Estimate and test the conditional and moderated mediation effects
- Assess sensitivity to unmeasured pretreatment confounding
- Visualize the results
- Applicable to a treatment of any scale, a binary or continuous mediator, a binary or continuous outcome, and one or more moderators of any scale.

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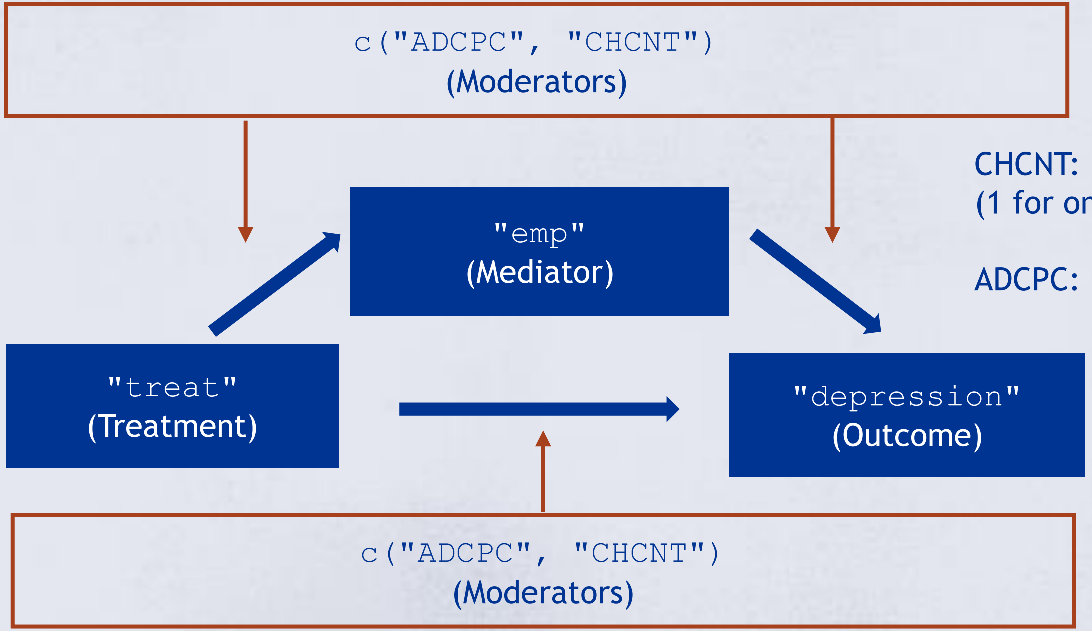
Hypothesized moderated mediation mechanism



CHCNT: baseline number of children (discrete)
(1 for one kid; 2 for two kids; 3 for three or more kids)

ADCPC: baseline welfare amount (continuous)

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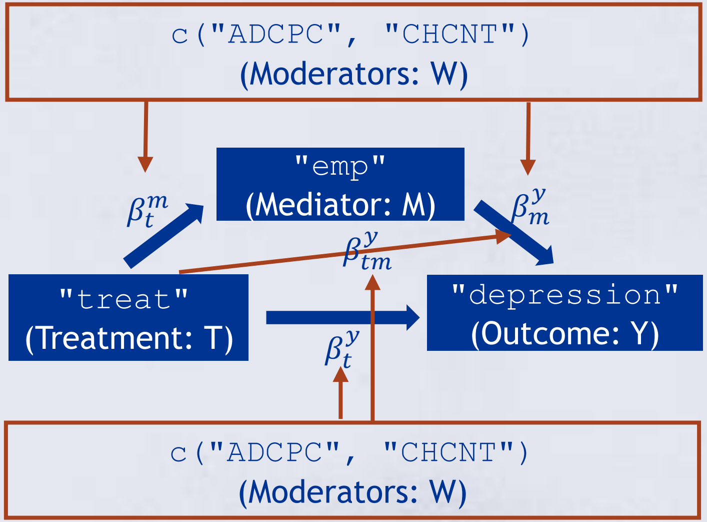
Models in the hierarchical form



$$M = \beta_0^m + \beta_t^m T + \mathbf{X}\boldsymbol{\beta}_x^m + \varepsilon_m, \varepsilon_m \sim N(0, \sigma_m^2)$$
$$Y = \beta_0^y + \beta_t^y T + \beta_m^y M + \beta_{tm}^y TM + \mathbf{X}\boldsymbol{\beta}_x^y + \varepsilon_y, \varepsilon_y \sim N\left(0, \sigma_y^2\right)$$

$$\begin{aligned}
\beta_0^m &= \beta_{00}^m + \boldsymbol{W}\boldsymbol{\beta}_{0w}^m \\
\beta_t^m &= \beta_{t0}^m + \boldsymbol{W}\boldsymbol{\beta}_{tw}^m \\
\beta_0^y &= \beta_{00}^y + \boldsymbol{W}\boldsymbol{\beta}_{0w}^y \\
\beta_t^y &= \beta_{t0}^y + \boldsymbol{W}\boldsymbol{\beta}_{tw}^y \\
\beta_m^y &= \beta_{m0}^y + \boldsymbol{W}\boldsymbol{\beta}_{mw}^y \\
\beta_{tm}^y &= \beta_{tm0}^y + \boldsymbol{W}\boldsymbol{\beta}_{tmw}^y
\end{aligned}$$

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Effect estimation and inference

```
data(newws)
results = modmed(data = newws,
                 treatment = "treat",
                 mediator = "emp",
                 outcome = "depression",
                 covariates.disc = c("emp_prior", "nevmar", "hispanic", "nohsdip"),
                 covariates.cont = c("workpref", "attitude", "depress_prior"),
                 moderators.disc = "CHCNT",
                 moderators.cont = "ADCPC",
                 m.model = list(


                                                    ),
                 y.model = list(




                                ),
                 comp.treatment.value = 1,
                 ref.treatment.value = 0,
                 comp.mod.disc.values = 3,
                 ref.mod.disc.values = 2,
                 comp.mod.cont.values = 5050,
                 ref.mod.cont.values = 5050,
                 m.scale = "binary",
                 y.scale = "continuous",
                 method = "mc", nmc = 1000, conf.level = 0.95, seed = 1)
```

Their default values are NULL.
E.g., no need to specify moderators.disc if there are no discrete moderators.

$$M = \beta_0^m + \beta_t^m T + \mathbf{X}\boldsymbol{\beta}_x^m + \varepsilon_m$$
$$\beta_0^m = \beta_{00}^m + \boldsymbol{W}\boldsymbol{\beta}_{\mathbf{0w}}^{\boldsymbol{m}}$$
$$\beta_t^m = \beta_{t0}^m + \boldsymbol{W}\boldsymbol{\beta}_{\boldsymbol{tw}}^{\boldsymbol{m}}$$
$$Y = \beta_0^y + \beta_t^y T + \beta_m^y M + \beta_{tm}^y TM + \mathbf{X}\boldsymbol{\beta}_x^y + \varepsilon_y$$
$$\beta_0^y = \beta_{00}^y + \boldsymbol{W}\boldsymbol{\beta}_{\mathbf{0w}}^{\boldsymbol{y}}$$
$$\beta_t^y = \beta_{t0}^y + \boldsymbol{W}\boldsymbol{\beta}_{\boldsymbol{tw}}^{\boldsymbol{y}}$$
$$\beta_m^y = \beta_{m0}^y + \boldsymbol{W}\boldsymbol{\beta}_{\boldsymbol{mw}}^{\boldsymbol{y}}$$
$$\beta_{tm}^y = \beta_{tm0}^y + \boldsymbol{W}\boldsymbol{\beta}_{\boldsymbol{tmw}}^{\boldsymbol{y}}$$

comp: comparison (t = 1 by default).
ref: reference (t' = 0 by default).

If one does not want to condition some moderators on specific values, one may specify their values to be NA.

Summarize analysis results

```
summary(object = results)
```

```
Treatment: treat

Mediator: emp

Outcome: depression

Pre-treatment confounders: emp_prior, nevmar, hispanic, nohsdip, workpref, attitude,
depress_prior

Moderators: CHCNT, ADCPC

Compare values of the treatment: 1

Reference values of the treatment: 0

Compare values of the moderators: 3, 5050

Reference values of the moderators: 2, 5050

Estimation method: Monte Carlo Method

Causal Effects:
           Estimate Std. Error 95% CI Lower 2.5% 95% CI Upper 2.5%
TE       0.47925508  0.6716924       -0.85981724        1.77596645
TIE     -0.76498887  0.3527762       -1.47218136       -0.09806794
PIE     -0.01629142  0.2270166       -0.44934204        0.45481519
PDE      1.24424395  0.7224715       -0.19591531        2.61923999
TDE      0.49554650  0.7115971       -0.91393794        1.90552911
INT     -0.74869745  0.4205389       -1.61948024        0.02738178
TE.ref   2.19848837  1.1361880        0.05964914        4.44545134
TIE.ref -0.95614534  0.6924313       -2.49873699        0.30463453
PIE.ref  0.16624820  0.4421947       -0.72998825        1.05244606
PDE.ref  3.15463371  1.2675048        0.70577443        5.58663299
TDE.ref  2.03224017  1.2354353       -0.40493093        4.44795983
INT.ref -1.12239354  0.8372979       -2.89434696        0.50936546
TE.dif  -3.26938152  1.5823285       -6.37740944       -0.06492951
TIE.dif  0.43697787  0.7531679       -0.95055948        2.10809748
PIE.dif -0.16362524  0.4688132       -1.05735349        0.74375372
PDE.dif -3.70635939  1.6847718       -6.92068720       -0.33509981
TDE.dif -3.10575628  1.6622477       -6.44243372        0.12034522
INT.dif  0.60060311  0.9031720       -1.09897932        2.53426161
---
CI is confidence interval constructed based on simulation of mediator and outcome model
parameters (number of simulations is 1000)
```

Population average effects

Conditional effects of the reference group

Moderated effects

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Interpretation of the results

- The total LFA effect is estimated to be 0.48 (SE = 0.67, 95% CI = [-0.86, 1.78]), which can be decomposed into
  - a pure (natural) direct effect, estimated to be 1.24 (SE = 0.72, 95% CI = [–0.20, 2.62]), about 16.07% of a standard deviation of the outcome in the control group; and
  - a total (natural) indirect effect, estimated to be -0.76 (SE = 0.35, 95% CI = [-1.47, -0.10]), about -9.88% of a standard deviation of the outcome in the control group.
- The pure direct effect indicates that, LFA would have increased maternal depression if one's employment experience is held at the level under the control condition, but not by a statistically significant amount.
- In contrast, the total indirect effect reflects that the LFA-induced increase in employment rate significantly reduced one's maternal depression, when the treatment is held at the LFA condition.
- The counteracting indirect and direct effects explained the insignificant total effect.

Interpretation of the results

- The total indirect effect can be further decomposed into
  - a pure indirect effect, which is estimated to be -0.02 (SE = 0.23, 95% CI = [-0.45, 0.45]); and
  - a natural treatment-by-mediator interaction effect, which is estimated to be -0.75 (SE = 0.42, 95% CI = [-1.62, 0.03]).
- The natural treatment-by-mediator interaction effect indicates that the LFA-induced increase in employment rate reduced maternal depression more under the LFA condition (i.e., total indirect effect) than under the control condition (i.e., pure indirect effect).
- Equivalently, the natural treatment-by-mediator interaction effect can also be viewed as the difference between the total direct effect and the pure direct effect, which indicates that LFA would have increased maternal depression to a smaller extent if holding one's employment experience under the LFA condition than if holding that under the control condition

Interpretation of the results

- Through the moderated mediation analysis, we further detected a significantly positive pure direct effect among those who had two children at baseline and received median level ($5050) of welfare in the year prior to randomization, which is estimated to be 3.15 (SE = 1.27, 95% CI = [0.71, 5.59]).
- This conditional pure direct effect is significantly higher than that of those with three children and $5,050 welfare in the year prior to randomization. The magnitude of the difference is estimated to be 3.71 (SE = 1.68, 95% CI = [0.34, 6.92]).

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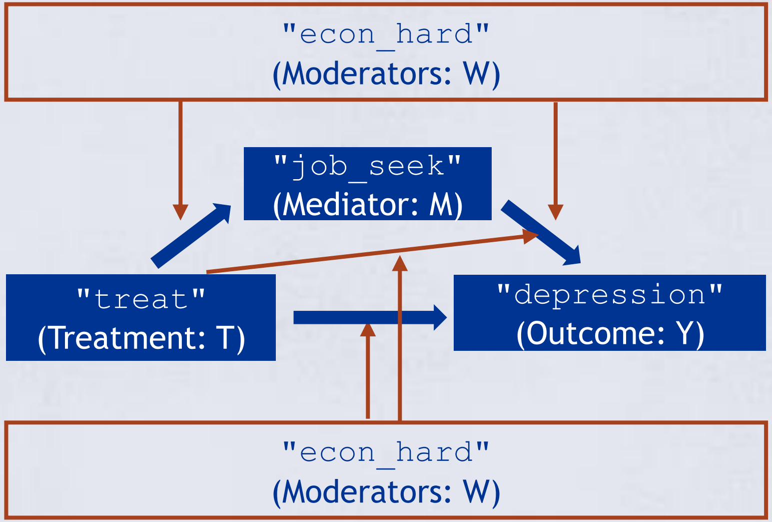
Exercise

- JOBS II is a randomized field experiment that investigates the efficacy of a job training intervention on unemployed workers. The program is designed to not only increase reemployment among the unemployed but also enhance the mental health of the job seekers.
- In the JOBS II field experiment, 1,801 unemployed workers received a pre-screening questionnaire and were then randomly assigned to treatment and control groups.
  - Those in the treatment group participated in job-skills workshops. In the workshops, respondents learned job-search skills and coping strategies for dealing with setbacks in the job-search process.
  - Those in the control condition received a booklet describing job-search tips.
- In follow-up interviews, continuous measures of job search self-efficacy and depressive symptoms were sequentially measured.

Exercise

- Import the data set by running the following code in R:
  - `jobs = write.csv("E:\\R\\jobs.csv")`
  - `# Replace the path with the path of the folder where you save the data.`
- Treatment: `treat`
- Mediator: `job_seek`, level of job-search self-efficacy with values from 1 to 5.
- Outcome: `depress2`, measure of depressive symptoms post-treatment.
- Moderator: `econ_hard`, baseline level of economic hardship with values from 1 to 5.
- Pretreatment covariates (a small set for illustration purpose):
  - `depress1` (continuous): Measure of depressive symptoms pre-treatment.
  - `sex` (discrete): 1 = female and 0 otherwise.
  - `age` (continuous): Age in years.

Exercise



Conduct the moderated mediation analysis based on the above diagram using the modmed function. Report the estimation and inference results of

1) TIE among those whose `econ_hard` = 1
2) the difference in TIE between those whose `econ_hard` = 5 and those whose `econ_hard` = 1

Exercise 1

- Please run the moderated mediation analysis by completing the following code.

```
results = modmed(data = jobs,
                 treatment = "treat",
                 mediator = "job_seek",
                 outcome = "depress2",
                 covariates.disc = "sex",
                 covariates.cont = c("age", "depress1"),
                 moderators.cont = "econ_hard",
                 m.model = list(),
                 y.model = list(),
                 comp.treatment.value = 1,
                 ref.treatment.value = 0,
                 comp.mod.cont.values = ,
                 ref.mod.cont.values = ,
                 m.scale = "continuous",
                 y.scale = "continuous",
                 method = "mc", nmc = 1000, conf.level = 0.95, seed = 1)
summary(object = results)
```

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Exercise 1 -- solution

```
results = modmed(data = jobs,
                 treatment = "treat",
                 mediator = "job_seek",
                 outcome = "depress2",
                 covariates.disc = "sex",
                 covariates.cont = c("age", "depress1"),
                 moderators.cont = "econ_hard",
                 m.model = list(intercept = "econ_hard", treatment = "econ_hard",
                 depress1 = NULL, age = NULL, sex = NULL),
                 y.model = list(intercept = "econ_hard", treatment = "econ_hard",
                 mediator = "econ_hard", tm = "econ_hard", depress1 = NULL, age =
                 NULL, sex = NULL),
                 comp.treatment.value = 1,
                 ref.treatment.value = 0,
                 comp.mod.cont.values =5,
                 ref.mod.cont.values =1,
                 m.scale = "continuous",
                 y.scale = "continuous",
                 method = "mc", nmc = 1000, conf.level = 0.95, seed = 1)
summary(object = results)
```

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Sensitivity analysis

```
sens.results = modmed.sens(object = results,
                           sens.effect = c("TIE", "PIE",
                           "TDE", "PDE","INT", "TIE.ref",
                           "PIE.ref", "PDE.ref", "TDE.ref",
                           "INT.ref", "TIE.dif", "PIE.dif",
                           "PDE.dif", "TDE.dif","INT.dif"),
                           range.b.m = NULL,
                           range.b.y = NULL,
                           grid.b.m = 10,
                           grid.b.y = 10,
                           U.scale = "binary",
                           p.u = 0.5,
                           t.rand = TRUE,
                           t.model = NULL,
                           t.scale = "binary",
                           b.t = NULL,
                           iter = 10,
                           nsim = 5,
                           ncore = 8)
```

sens.effect can also be specified as a subvector of the default. It does not matter how the effects are ordered.

This is the value range of the sensitivity parameters. The values are automatically generated if NULL is specified.

They are divided into a grid.b.m-by-grid.b.y grid, which is 10-by-10 by default. The finer the grid, the smoother the sensitivity analysis plot.

The conditional distribution of U also relies on the marginal distribution of U, which is assumed to be binary (U.scale = "binary") with Pr(U = 1) = 0.5 (p.u = 0.5) by default. One can change U.scale to be "continuous" for a continuous U.

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Sensitivity analysis

```
sens.results = modmed.sens(object = results,
                           sens.effect = c("TIE", "PIE",
                           "TDE", "PDE","INT", "TIE.ref",
                           "PIE.ref", "PDE.ref", "TDE.ref",
                           "INT.ref", "TIE.dif", "PIE.dif",
                           "PDE.dif", "TDE.dif","INT.dif"),
                           range.b.m = NULL,
                           range.b.y = NULL,
                           grid.b.m = 10,
                           grid.b.y = 10,
                           U.scale = "binary",
                           p.u = 0.5,
                           t.rand = TRUE,
                           t.model = NULL,
                           t.scale = "binary",
                           b.t = NULL,
                           iter = 10,
                           nsim = 5,
                           ncore = 8)
```

When treatment is not randomized, we need to specify another sensitivity parameter, which is the slope of unmeasured confounder in the standardized treatment model.

One may use the standardized coefficient estimates of the observed covariates in the treatment model as referent values for the specification of b.t.

If there are multiple values of b.t to be assessed, one may conduct the sensitivity analysis multiple times to assess the influence of each value of b.t, one at a time.

By default, the treatment is randomized (t.rand =TRUE). If treatment is not randomized (t.rand = FALSE), one needs to specify t.model in the same way as specifying m.model and y.model, because a treatment model is required for the derivation of the conditional distribution of the unmeasured pretreatment confounder U.

To speed up the calculation, the package allows parallel computing by setting the number of CPU cores via ncore. detectCores() can be used to detect the total number of cores available on a computer. To use the function, please install and load the package “parallel” first. It is not recommended to use up all the cores. At least one core should be saved to run other programs on the computer while you are running the R program

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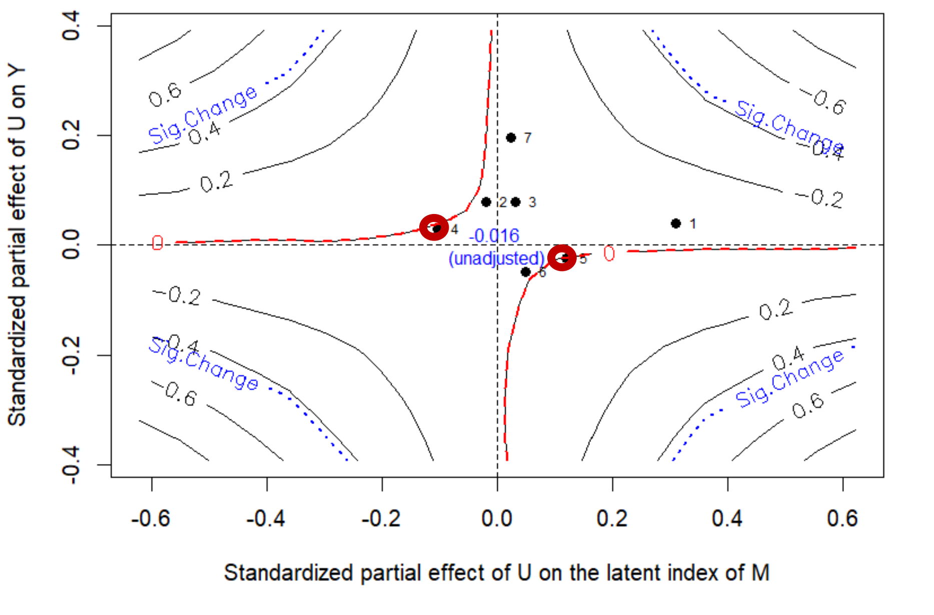
Sensitivity analysis results

```
sens.plot(object = results,
          sens.results = sens.results,
          effect = "PIE")
```

Check the plot for each effect one at a time.



Sensitivity Analysis Plot for the Pure Indirect Effect

1-7 are respectively comparable to emp_prior, nevmar, hispanic, nohsdip, workpref, attitude, and depress_prior.

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Interpretation of the results

- The figure shows that an additional adjustment of a binary unmeasured pretreatment confounder U with Pr(U=1)=0.5 would reverse the sign of PIE as long as the confounding role of U is as strong as one's baseline educational attainment (nohsdip) or work preference (workpref).
- Nevertheless, for the significance of PIE to be altered, U must be much stronger than the strongest observed pretreatment confounder.
- Because we have controlled for the most important pretreatment confounders in theory, it is almost impossible for the remaining confounders to reverse the significance of PIE even collectively. Hence, the sign of PIE may be sensitive but its significance is more robust.
- Similarly, we can obtain the sensitivity plots for the other effects, which are mostly robust to unmeasured pretreatment confounding.

Exercise 2

- Conduct a sensitivity analysis to evaluate whether TIE.ref and TIE.dif are sensitive to a potential violation of the identification assumption by completing the following code. For illustration purpose, please specify grid.b.m and grid.b.y to be 2. Their values need to be increased in real data analysis.

```
sens.results = modmed.sens(object = ,
                           sens.effect = c("", ""),
                           range.b.m = NULL,
                           range.b.y = NULL,
                           grid.b.m = ,
                           grid.b.y = ,
                           U.scale = "binary",
                           p.u = 0.5,
                           t.rand = TRUE,
                           t.model = NULL,
                           t.scale = "binary",
                           b.t = NULL,
                           iter = 10,
                           nsim = 5,
                           ncore = )
sens.plot(object = results,
          sens.results = sens.results,
          effect = "")
```

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Exercise 2 -- solution

```
sens.results = modmed.sens(object = results,
                           sens.effect = c("TIE.ref", "TIE.dif"),
                           range.b.m = NULL,
                           range.b.y = NULL,
                           grid.b.m = 2,
                           grid.b.y = 2,
                           U.scale = "binary",
                           p.u = 0.5,
                           t.rand = TRUE,
                           t.model = NULL,
                           t.scale = "binary",
                           b.t = NULL,
                           iter = 10,
                           nsim = 5,
                           ncore = detectCores()-1)
sens.plot(object = results,
          sens.results = sens.results,
          effect = "TIE.ref")
sens.plot(object = results,
          sens.results = sens.results,
          effect = "TIE.dif")
```

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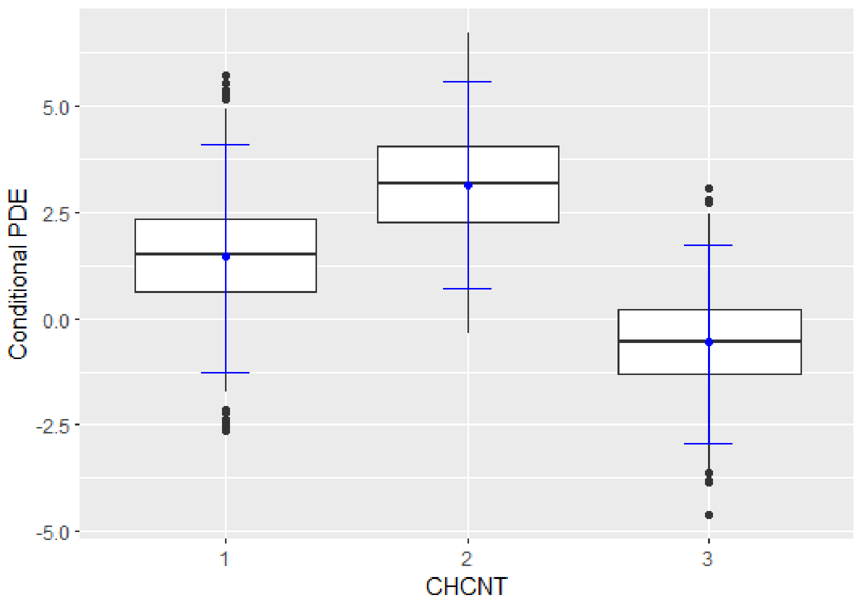
Visualization of results

```
modmed.plot(object = results,
            effect = "PDE",
            moderator = "CHCNT",
            other.mod.cont.values = 5050)
```

effect can be "TE", "TIE", "PDE", "PIE", "TDE", or "INT“.

If one does not want to condition some moderators on specific values, one may specify their values to be NA.



Conditional PDE as a function of CHCNT given ADCPC = 5050.

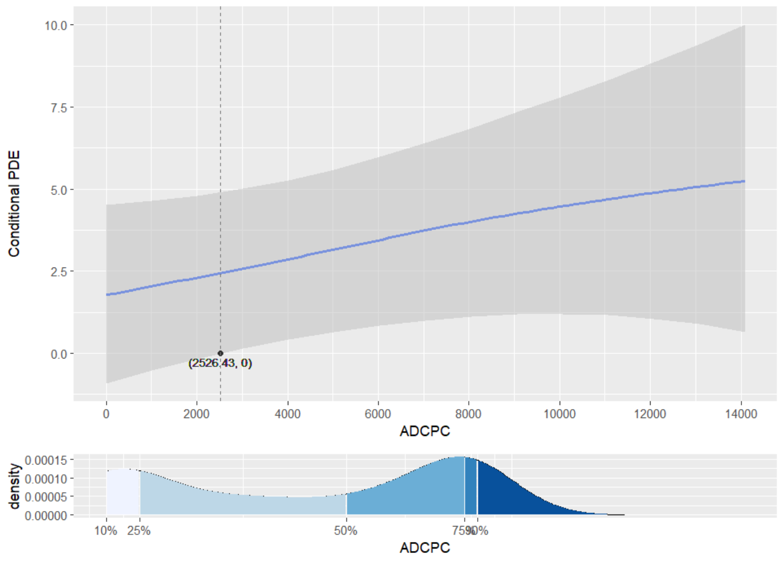
Interpretation of the results

- Among those who received $5050 welfare in the year before randomization, the pure direct effect of LFA on maternal depression is estimated to be positive among those with one or two children at baseline, while significant only among those with two children.
- In contrast, among those with three or more children, LFA would have reduced maternal depression if not changing one's employment experience, but not by a statistically significant amount.
- This matches and supplements the numerical summary obtained from the summary() function.

Visualization of results

```
modmed.plot(object = results,
            effect = "PDE",
            moderator = "ADCPC",
            other.mod.disc.values = 2,
            is.dist.moderator = TRUE,
            probs = c(0.1, 0.25, 0.5, 0.75, 0.9),
            ncore = 8)
```

Five percentile lines are added to the distribution of the moderator, which facilitates the evaluation of conditional effects at given percentiles of each continuous moderator.



1. Top: Conditional PDE as a function of ADCPC given CHCNT = 2.
2. Bottom: Sample distribution of ADCPC given CHCNT = 2.

Interpretation of the results

- Among those who had two children at baseline, the pure direct effect of LFA on maternal depression increased as one received more welfare amount in the year prior to randomization.
- The effect is significant when the welfare amount is larger than $2526.
- The sample distribution of the welfare amount indicates that about 70% of the participants with two children are in the significant region.

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Exercise 3

- Please visualize how the total indirect effect of the job training intervention on depression transmitted through job search self-efficacy varied by `econ_hard` by completing the following code.

```
modmed.plot(object = results,
            effect = "",
            moderator = "",
            is.dist.moderator = TRUE,
            probs = c(0.1, 0.25, 0.5, 0.75, 0.9),
            ncore = )
```

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Exercise 3 -- solution

```
modmed.plot(object = results,
            effect = "TIE",
            moderator = "econ_hard",
            is.dist.moderator = TRUE,
            probs = c(0.1, 0.25, 0.5, 0.75, 0.9),
            ncore = detectCores()-1)
```

Recommended analytic procedure

- We recommend that researchers utilize the graphical tool for an overview of the influence of a moderator on the magnitude, sign, and significance of an effect.
- If the effect linearly changes with a continuous moderator, one can assess if the effect is significantly moderated by testing the difference in the effect between any two moderator values that are one unit apart.
- Otherwise, one can locally assess moderated mediation by testing the difference in the effect between two given values of the moderator.

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Summary

Advantages

- By assessing how an intervention worked differently across individuals, we can better understand the intervention's efficacy and make individual-specific modifications of the intervention design and implementation. Correspondingly, we can improve and tailor interventions to different individuals and thus enhance educational equity.
- Specifying the models in the hierarchical form eases model specification and result interpretation.
- The visualization of the analysis results intuitively represents how a causal mediation effect varies by a moderator.
- A sensitivity analysis is incorporated to evaluate the sensitivity of the original analysis results to potential unmeasured pretreatment confounding.

Discussion

- The regression-based causal moderated mediation analysis method relies on correct model specifications. We may fit nonparametric models or machine learning models to allow for more robust and flexible modeling.
- The analysis assumes no posttreatment confounding.
- Here we focus on a pretreatment moderator.
  - If a moderator is concurrent with the mediator, the estimation and inference stay the same, while the definitions and identification assumptions change.
  - If a moderator is also a sequential mediator, we need to conduct a mediation analysis for sequential mediators that interact with each other (Daniel et al., 2015).
- Extensions can be made for longitudinal or multilevel moderated mediation analysis, or to account for measurement error.

Writing A Causal (Moderated) Mediation Analysis Paper

[Qin (in press)]

Introduction

- It is essential to clarify the hypothesized mediation mechanism and its heterogeneity based on a literature review of theoretical rationale or supporting evidence for
  - the treatment affects the mediator, which subsequently affects the outcome;
  - how the mediation mechanism varies by individuals or contexts.
- It is also necessary to list research questions, such as
  - whether the mediator mediates the relationship between the treatment and the outcome;
  - how much of the treatment effect is transmitted through the mediator;
  - how the mediation mechanism varies by individuals or contexts, etc.

Methods

- This section includes the study design, participants, sample size, and measures, including the treatment, mediator, outcome, and a set of pretreatment confounders of the mediator-outcome relationship (and the treatment-mediator and treatment-outcome relationships if the treatment is not randomized).
- It is particularly important to clarify when the variables were measured. Under the principle of temporal precedence (i.e., the cause precedes the effect), the treatment, mediator, and outcome should be measured in order, rather than simultaneously, to allow the treatment to generate an impact on the mediator and subsequently influence the outcome, as illustrated in the NEWWS example.

Methods

- The pretreatment covariates, as the name suggests, should be measured before the treatment. If a pretreatment covariate does not vary over time, it can be measured at any time.
- The current causal moderated mediation analysis requires that the moderator is pretreatment in nature. A key question is how to choose moderators. The commonly recommended approach is built upon substantive knowledge about which pretreatment covariates are most likely to show evidence for heterogeneity (VanderWeele, 2015) of the mediation mechanism.

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Methods

- To minimize the possibility of violating the assumption of no post-treatment confounding, one may choose the time point of measurement for the mediator to be relatively close to that for the treatment (VanderWeele & Vansteelandt, 2009, page 462).
- It is worth noting that the indirect effect may vary when the mediator is measured at a different time point.
  - For example, the mediating role of whether a mother was employed during the first year after randomization underlying the LFA impact on maternal depression at the end of the second year may differ from that of whether a mother was employed during the two-year period after randomization.
  - The latter can better capture the entire process, but at a higher risk of violating the no post-treatment confounding assumption.

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Methods

- In addition, in this section, it is essential to
  - describe the chosen causal (moderated) mediation analysis method;
  - rationalize the choice of the method;
  - clarify the underlying assumptions;
  - discuss the plausibility of the assumptions;
  - justify the methods used to handle missing data.

Analysis results

- This section reports the estimation and inference results of the causal (moderated) mediation analysis.
- The effect sizes reflect the practical significance.
- The p-values or confidence intervals reveal the statistical significance.
- Intuitive interpretations of the effects are needed to better answer the research questions proposed in the introduction section.

Sensitivity analysis

- A causal (moderated)mediation analysis is incomplete without a sensitivity analysis.
- It is crucial to report how robust the reported analysis results are to potential unmeasured pretreatment confounding.

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Discussion

- Summarize the findings.
- State the implications of the results for practice, policy, and science.
- Discusses limitations of the analysis, such as
  - a possible violation of the SUTVA assumption, the positivity assumption, or the assumption of no post-treatment confounding,
  - failures to account for measurement error,
  - vulnerability to model misspecifications, etc.
- It is also necessary to clarify how these limitations would affect the validity of the conclusions.

Major reference

- Qin, X. & Wang, L. (2024). Causal moderated mediation analysis: methods and software. *Behavior Research Methods*, 56(3), 1314-1335.
- A guide on R implementation for causal moderated mediation analysis

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References on other topics

- Qin, X. (in press). Introduction to causal mediation analysis. Asia Pacific *Education Review*. (Invited paper for a special issue on causal research designs and analysis in education.)
- Qin, X. (2024). Sample size and power calculations for causal mediation analysis: a tutorial and Shiny app. *Behavior Research Methods*, 56(3), 1738-1769.

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References on other topics

- Evaluations of multivalued treatments (Hong (2015) Chapter 5)
- Multiple mediators (VanderWeele (2015) Chapter 5; Hong (2015) Chapters 13.2, 13.3)
- Mediation analysis with time-varying exposures and mediators (VanderWeele (2015) Chapter 6)
- Direct and indirect effects in health disparities research (VanderWeele (2015) Chapter 7.4)
- Spillover effects (VanderWeele (2015) Chapter 15; Hong (2015) Chapters 14, 15)
- Posttreatment confounder: When there are posttreatment confounders, natural direct and indirect effects cannot be point-identified.
  - Hong, Yang, Qin (2023) developed a sensitivity analysis strategy to provide a bound for the effects.
  - Interventional perspective
    - VanderWeele et al. (2014) defined a randomized interventional analogue of natural direct and indirect effects that are identified in this setting.
    - Nguyen et al. (2021) clarified the difference between the definitions that we have learned and the randomized interventional analogue of natural direct and indirect effects.
    - Analysis can be done via https://bs1125.github.io/CMAverse/articles/post_exposure_confounding.html

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- VanderWeele, T. J., & Vansteelandt, S. (2009). Conceptual issues concerning mediation, interventions and composition. *Statistics and Its Interface*, 2, 457–468.
- VanderWeele, T. J., Vansteelandt, S., & Robins, J. M. (2014). Effect decomposition in the presence of an exposure-induced mediator-outcome confounder. *Epidemiology*, 25(2), 300-306.

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