Mediation analysis first step: Defining effects based on what we want to learn

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Synopsis

- Original desire: understand mechanisms of effect of A on Y
  - effect through a causal pathway via an intermediate variable M
  - total effect = direct + indirect components
- With this desire
  - Effect were traditionally model-centric, eg indirect effect $= ab$, where a, b are two regression coefs
  - Causal inference revised these effects using potential outcomes, freeing them from the models – *natural (in)direct effects*
- Causal inference brings in the idea of sequential intervention
  - Another genre of effects – *interventional effects*
  - Fit a different desire: effects of hypothetical conditions – in intervention research, disparity research
- Our proposal: carefully choose the target effect (*estimand*) based on what we want to learn

The estimand should drive the analysis

- *define*: define the target estimand – what we want to learn
- *identify*: assess its identifiability – given study design, assumptions
- *estimate*: estimate or test it – using statistical methods

Clarity on the estimand leads to clarity in interpreting analysis results

Effect definitions $\leftarrow$ research questions

Many effects and effect types

Which one best matches my research question?

May require clarifying vague research questions

If the research question is about explaining the causal effect of exposure on outcome

eg

- what are the mechanisms of this effect?
- what part of this effect is due to the exposure's influence on this intermediate variable and what part is not?
- is the effect partly due to the exposure's influence on this intermediate variable?

If the research question is about explaining the causal effect of exposure on outcome

in mediation lingo,

- what are the mediators of this effect?
- what is the indirect effect (mediated by this variable) and what is the direct effect?
- is this variable a mediator of this effect?

If the research question is about explaining the causal effect of exposure on outcome

then the closest estimands are *natural (in)direct effects*

- they decompose the total effect
- a NIE can be interpreted as an effect on the outcome *of the exposure's effect on the mediator*

decompositions are not unique

Notation and consistency

$$A \quad \ldots\ldots \quad M \quad \ldots\ldots \quad Y$$

Observed variables:	A	binary exposure (0/1)
	M	mediator
	Y	outcome
Potential variables:	M_a	$a = 0, 1$
	Y_a	
	Y_{am}	m is a mediator value
	$Y_{aM_{a'}}$	

Consistency assumptions: (connecting potential and observed variables)	if $A = a$	$M = M_a$
		$Y = Y_a = Y_{aM} = Y_{aM_a}$
	if $A = a, M = m$	$Y = Y_a = Y_{aM} = Y_{am}$
	if $M(a') = m$	$Y_{aM_{a'}} = Y_{am}$

Natural (in)direct effects

Defined at individual level, decompose individual total effect

$$\begin{aligned} TE &= Y_1 - Y_0 \\ &= Y_{1M_1} - Y_{0M_0} \end{aligned}$$

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2 decompositions

- direct-indirect: $TE = \underbrace{Y_{1M_1} - Y_{1M_0}}_{NIE_1} + \underbrace{Y_{1M_0} - Y_{0M_0}}_{NDE_0}$
- indirect-direct: $TE = \underbrace{Y_{1M_1} - Y_{0M_1}}_{NDE_1} + \underbrace{Y_{0M_1} - Y_{0M_0}}_{NIE_0}$

NIE $=$ an effect on the outcome *of the exposure's effect on the mediator*

NDE $=$ an effect of the exposure when holding the mediator at a natural value

Natural (in)direct effects

Target average effects (individual effects not identified and not of interest)

- direct-indirect: $\mathrm{TE} = \underbrace{\mathrm{E}[Y_1] - \mathrm{E}[Y_{1M_0}]}_{\mathrm{NIE}_1} + \underbrace{\mathrm{E}[Y_{1M_0}] - \mathrm{E}[Y_0]}_{\mathrm{NDE}_0}$
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Which decomposition to use? – discussion in paper

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Not identified if exist mediator-outcome confounders influenced by exposure now another effect type for another question type

If the research question is a *what-if* question

eg

- in intervention development research: what if the program is modified
    - removing elements that affect the mediator
    - retaining only elements that affect the mediator
    - some other way
- in disparities research: what if could shift the distribution of a factor that contributes to disparity

then want to consider the class of *interventional effects*

Interventional effects

Lage class, incl. total effect, controlled direct effect, generalized direct effects, interventional (in)drect effects, many other effects, NOT natural (in)direct effects

An effect in this class contrasts

- a (hypothetical) active intervention condition
- a comparison intervention (or no intervention) condition

An (hypothetical) intervention condition

- sets exposure and/or mediator each to a specific value or distribution that is known or is identified (based on data observed in current study)
- does not change anything else

Selecting an interventional effect

2 key questions:

- Which condition best matches the *what-if* condition of scientific interest?
- What is the most appropriate comparison condition?

Note that an interventional effect

- generally does not tell us exactly about a *realistic* intervention

  BUT
- does tell us about an *ideal* intervention

- our job to judge how rough or fine the approximation is

Some examples

Controlled and generalized direct effects

A	M	Y
traffic safety intervention	bike helmet use	injury

In the context of new law requiring helment use

assuming 100% compliance, the effect of the intervention in the new context is a controlled direct effect:

$$\text{CDE}(100) = \text{E}[Y(1, 100)] - \text{E}[Y(0, 100)]$$

assuming compliance about 75% $\pm$ 15%, and representing this distribution by $\mathcal{M}$, the intervention's effect in the new context is a generalized direct effect:

$$\text{GDE}(\mathcal{M}) = \text{E}[Y(1, \mathcal{M})] - \text{E}[Y(0, \mathcal{M})]$$

Effect of intervention if modified to remove indirect effect elements

$$C \quad \cdots\cdots\cdots\cdots \quad A \quad \cdots\cdots\cdots\cdots \quad M \quad \cdots\cdots\cdots\cdots \quad Y$$

safer sex intervention | self-efficacy | protection behavior

$$\mathrm{E}[Y(1, \mathcal{M}(0 \mid C))] - \mathrm{E}[Y(0)]$$

The active intervention condition here sets the exposure to 1, but sets the mediator to the distribution of $M(0)$ (conditional on pre-exposure covariates)

Note this is different from setting the mediator to $M(0)$

The squiggly $\mathcal{M}$ indicates the randomness of the mediator values assigned

Effect of intervention if modified to remove direct effect elements

$$C \quad \cdots\cdots\cdots\cdots \quad A \quad \cdots\cdots\cdots\cdots \quad M \quad \cdots\cdots\cdots\cdots \quad Y$$

	safer sex intervention	access to protection	protection behavior

$$\mathrm{E}[Y(0, \mathcal{M}(1 \mid C))] - \mathrm{E}[Y(0)]$$

The active intervention condition here sets the exposure to 0, but sets the mediator to the distribution of $M(1)$ (conditional on pre-exposure covariates)

Effect of alternative intervention that affects treatment but not screening for depression

C	··· ··· ··· ···	A	··· ··· ··· ···	L	··· ··· ··· ···	M	··· ··· ··· ···	Y
		intervention with providers		depression screening		depression treatment		patient outcome

$$E[Y(0, L(0), \mathcal{M}(1, L(0) \mid C))] - E[Y(0)]$$

Here the notation $\mathcal{M}(1, L(0) \mid C)$ means the distribution of the mediator had A been set to 1 and L been set to the value of $L(0)$

Interventional (in)direct effects

Cousins of natural (in)direct effects that are well known but arguable not as relevant as some of the effects mentioned above

$$\mathrm{IDE}(\cdot 0) = \mathrm{E}[Y(1, \mathcal{M}(0|C))] - \mathrm{E}[Y(0, \mathcal{M}(0|C))]$$
$$\mathrm{IDE}(\cdot 1) = \mathrm{E}[Y(1, \mathcal{M}(1|C))] - \mathrm{E}[Y(0, \mathcal{M}(1|C))]$$

$$\mathrm{IIE}(0\cdot) = \mathrm{E}[Y(0, \mathcal{M}(1|C))] - \mathrm{E}[Y(0, \mathcal{M}(0|C))]$$
$$\mathrm{IIE}(1\cdot) = \mathrm{E}[Y(1, \mathcal{M}(1|C))] - \mathrm{E}[Y(1, \mathcal{M}(0|C))]$$

Note these are equal to natural (in)direct effects in the special case with no intermediate confounders

What if could bring the bullying experienced by sexual minority adolescents down to half-way between their actual level and that of sexual majority adolescents

$$C \cdots\cdots\cdots\cdots A \cdots\cdots\cdots\cdots M \cdots\cdots\cdots\cdots Y$$

	sexual minority status	bullying experienced	wellbeing

$$\mathrm{E}[Y(1, \mathcal{M}(0.5|C)) \mid A = 1] - \mathrm{E}[Y(1) \mid A = 1]$$

This class of interventional effects allows flexible definition of effects based on the question of interest

To sum up

Wide range of effect definitions

- natural (in)direct effects
- very broad class of interventional effects

Flexibility in selecting/defining effects to match research questions in prevention science

THANK YOU