Causal mediation analysis: Estimation of effects for the single mediator case - continued

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Session overview

Estimation for the single mediator case - continued

- natural direct and indirect effects based on other combinations of exposure/mediator/outcome models
- controlled direct effect in the presence of post-exposure confounder
- survival outcome (if time permits)

Natural direct and indirect effects based on other combinations of exposure/mediator/outcome models

i.e., other than the mediator-and-outcome combination

Recall the simpler case: exposure $\longrightarrow$ outcome

exposure A, outcome Y, confounders X (for simplicity, binary A, continuous Y)

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To estimate the average causal effect, our options are: to rely on

1. a model of the outcome: $\mathrm{E}[Y|A,X] = \beta_0 + \beta_1(A) + \beta_2(X) + \beta_3(A,X)$
    - plug in for A to get conditional causal effect: $\hat{\mathrm{E}}[Y|1,X] - \hat{\mathrm{E}}[Y|0,X]$ and average over X to get marginal/average causal effect (if interaction)
    - assumes correctly specified outcome model: no unobserved confounders, correct functional forms, holds for full range of X

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2. a model of exposure assignment: $g[\mathrm{P}(A = 1|X)] = \gamma_0 + \gamma_1(X)$
   - estimate PS, weight/match based on PS to obtain balance on X, and take the difference between the means of Y as the average causal effect
     - if weighting, $W_i = \frac{1}{\hat{\mathrm{P}}(A=A_i|X=X_i)}$, or $W_i = \frac{\hat{\mathrm{P}}(A=A_i)}{\hat{\mathrm{P}}(A=A_i|X=X_i)}$ (stabilized)
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   - assumes correct specification of exposure assignment model
3. both models
   - fit exposure assignment model and use it to weight/match to obtain balance on X, then fit outcome model to weighted/matched sample
   - doubly robust: requires only one of the two models to be correctly specified (2 chances to get it right)

This suggests for the mediation case

with exposure A, mediator M, outcome Y, confounders X

to estimate the average causal effect, we should have the options of relying on

1. a model for the mediator and a model for the outcome
   - methods discussed so far based on the mediation formula
2. a model for the exposure and a model for the outcome
3. a model for the exposure and a model for the mediator
4. three models for the exposure, mediator and outcome

Modeling the exposure and the outcome: a weighting and imputation method (VanderWeele & Vansteelandt 2013)

- proposed for the multiple-mediator situation, but also applies to the single-mediator case
- targets marginal natural effects
- strategy:
  - impute Y_{0M_1} and Y_{1M_0} based on a model for the outcome
  - adjust for confounding via inverse-probability-of-exposure weighting

Modeling the exposure and the outcome (CORRECTED): a weighting and imputation method (VanderWeele & Vansteelandt 2013)

Specifically,

- fit exposure assignment model, e.g., $g[\mathrm{P}(A=1|X=x)] = \gamma_0 + \gamma_1 x$
  - take weighted average of the outcomes in the exposed group to estimate $\mathrm{E}[Y_{1M_1}]$, using the weights $\frac{\mathrm{P}(A=1)}{\mathrm{P}(A=1|X=X_i)}$
  - take weighted average of the outcomes in the unexposed group to estimate $\mathrm{E}[Y_{0M_0}]$, using the weights $\frac{\mathrm{P}(A=0)}{\mathrm{P}(A=0|X=X_i)}$
- fit outcome model, e.g.,
  $\mathrm{E}[Y|A=a, M=m, X=x] = \beta_0 + \beta_1 a + \beta_2 m + \beta_3 am + \beta_4 x$
  - using exposed individuals, combine their mediator values with exposure 0 to predict/impute new outcomes, then take the weighted average to predict $\mathrm{E}[Y_{0M_1}]$, using the weights $\frac{\mathrm{P}(A=1)}{\mathrm{P}(A=1|X=x_i)}$
  - using unexposed individuals, combine their mediator values with exposure 1 to predict/impute new outcomes, then take the weighted average to predict $\mathrm{E}[Y_{1M_0}]$, using the weights $\frac{\mathrm{P}(A=0)}{\mathrm{P}(A=0|X=x_i)}$
- use the estimated $\mathrm{E}[Y_{1M_1}]$, $\mathrm{E}[Y_{0M_0}]$, $\mathrm{E}[Y_{0M_1}]$ and $\mathrm{E}[Y_{1M_0}]$ to compute NIEs and NDEs on scale of choice

Modeling the exposure and the outcome: a weighting and imputation method (VanderWeele & Vansteelandt 2013)

- does not requiring modeling the mediator, a nice feature in the multiple-mediator case (next session)
- requires that the exposure model and the outcome model are both correctly specified

Modeling exposure and mediator assignment: imputation and weighting (Hong 2010; Lange, Vansteelandt, Bekaert 2012)

Suppose we observe all 4 types of potential outcomes Y_{1M_1}, Y_{0M_0}, Y_{0M_1}, Y_{1M_0}.

We could represent such data as

observation	potential outcome $Y_{\mathcal{A}_1 M_{\mathcal{A}_2}}$	first index $\mathcal{A}_1$	second index $\mathcal{A}_2$
i	$Y_i(1, M_i(1))$	1	1
j	$Y_j(1, M_j(0))$	1	0
k	$Y_k(0, M_k(0))$	0	0
l	$Y_l(0, M_l(1))$	0	1

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If we did not have to worry about confounding, we could simply fit the model

$$\mathrm{E}[Y_{\mathcal{A}_1 M_{\mathcal{A}_2}}] = \theta_0 + \theta_1 \mathcal{A}_1 + \theta_2 \mathcal{A}_2 + \theta_3 \mathcal{A}_1 \mathcal{A}_2$$

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If we did not have to worry about confounding, we could simply fit the model

$$E[Y_{\mathcal{A}_1 M_{\mathcal{A}_2}}] = \theta_0 + \theta_1 \mathcal{A}_1 + \theta_2 \mathcal{A}_2 + \theta_3 \mathcal{A}_1 \mathcal{A}_2$$

This MSM is a *natural effects* model (Vansteelandt, Bekaert, Lange 2012) because

$$\begin{aligned} E[Y_{1M_1}] &= \theta_0 + \theta_1 + \theta_2 + \theta_3 \\ E[Y_{0M_0}] &= \theta_0 \\ E[Y_{1M_0}] &= \theta_0 + \theta_1 \\ E[Y_{0M_1}] &= \theta_0 + \theta_2 \end{aligned} \quad \text{and} \quad \begin{aligned} \text{NDE}(\cdot 0) &= \theta_1 \\ \text{NDE}(\cdot 1) &= \theta_1 + \theta_3 \\ \text{NIE}(0 \cdot) &= \theta_2 \\ \text{NIE}(1 \cdot) &= \theta_2 + \theta_3 \end{aligned}$$

This is equivalent to simply contrasting $E[Y_{1M_1}]$, $E[Y_{0M_0}]$, $E[Y_{0M_1}]$ and $E[Y_{1M_0}]$.

Modeling exposure and mediator assignment: imputation and weighting (Hong 2010; Lange, Vansteelandt, Bekaert 2012)

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We could represent such data as

observation	potential outcome $Y_{\mathcal{A}_1 M_{\mathcal{A}_2}}$	first index $\mathcal{A}_1$	second index $\mathcal{A}_2$
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j	$Y_j(1, M_j(0))$	1	0
k	$Y_k(0, M_k(0))$	0	0
l	$Y_l(0, M_l(1))$	0	1

If the outcome is binary, we could use the natural effects model

$$\text{logit}[\text{P}(Y_{\mathcal{A}_1 M_{\mathcal{A}_2}} = 1)] = \theta_0 + \theta_1 \mathcal{A}_1 + \theta_2 \mathcal{A}_2 + \theta_3 \mathcal{A}_1 \mathcal{A}_2$$

which implies

$$\text{NDE}^{\text{OR}}(\cdot 0) = e^{\theta_1}$$
$$\text{NDE}^{\text{OR}}(\cdot 1) = e^{\theta_1 + \theta_3}$$
$$\text{NIE}^{\text{OR}}(0 \cdot) = e^{\theta_2}$$
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Modeling exposure and mediator assignment: imputation and weighting (Hong 2010; Lange, Vansteelandt, Bekaert 2012)

With survival data

observation	potential survival time $T_{\mathcal{A}_1 M_{\mathcal{A}_2}}$	censoring C	first index $\mathcal{A}_1$	second index $\mathcal{A}_2$
i	$T_i(1, M_i(1))$	C_i	1	1
j	$T_j(1, M_j(0))$	C_j	1	0
k	$T_k(0, M_k(0))$	C_k	0	0
l	$T_l(0, M_l(1))$	C_l	0	1

we could use a relative hazards model for the natural effects model

$$\log[\lambda_{\mathcal{A}_1 M_{\mathcal{A}_2}}(t)] = \log[\lambda_{0M_0}(t)] + \theta_1\mathcal{A}_1 + \theta_2\mathcal{A}_2 + \theta_3\mathcal{A}_1\mathcal{A}_2$$

which implies

$$\mathrm{NDE}^{\mathrm{HR}}(\cdot 0) = e^{\theta_1}$$
$$\mathrm{NDE}^{\mathrm{HR}}(\cdot 1) = e^{\theta_1+\theta_3}$$
$$\mathrm{NIE}^{\mathrm{HR}}(0\cdot) = e^{\theta_2}$$
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and perhaps a relative times model as well.

Modeling exposure and mediator assignment: imputation and weighting (Hong 2010; Lange, Vansteelandt, Bekaert 2012)

Problem 1/2: Two types of potential outcomes (Y_{0M_1}, Y_{1M_0}) are not observed.
Solution: Impute based on values of the observed ones.

obs	$\mathcal{A}_1$	$\mathcal{A}_2$	$Y_{\mathcal{A}_1 M_{\mathcal{A}_2}}$	$M_{\mathcal{A}_2}$	X
i	1	1	$Y_i(1, M_i(1)) = y^*$	$M_i(1) = m^*$	x^*
j	1	0	$Y_j(1, M_j(0)) = ?$	$M_j(0) = ?$	?
k	0	0	$Y_k(1, M_k(0)) = y^{**}$	$M_k(0) = m^{**}$	x^{**}
l	0	1	$Y_l(1, M_l(1)) = ?$	$M_l(1) = ?$	?

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When making identification assumptions i1-2/c1-4, we are saying that the outcomes are dependent on treatment assigned, mediator assigned and X, based on one rule that applies across the different potential worlds.

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We don't want to guess what this rule is, but know that it is encoded in the observed data from persons i ($X = x^*, \mathcal{A}_1 = 1, M_{\mathcal{A}_2} = m^*, Y_{\mathcal{A}_1 M_{\mathcal{A}_2}} = y^*$) and persons k ($X = x^{**}, \mathcal{A}_1 = 0, M_{\mathcal{A}_2} = m^{**}, Y_{\mathcal{A}_1 M_{\mathcal{A}_2}} = y^{**}$). We want to preserve this rule when imputing for persons j and persons k. The simplest is to borrow the observed values.

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Modeling exposure and mediator assignment: imputation and weighting (Hong 2010; Lange, Vansteelandt, Bekaert 2012)

Problem 2/2: Confounding. Solution: Adjustment by weighting.

$$W_i = W_{1i} \cdot W_{2i} = \frac{\mathrm{P}(A = \mathcal{A}_{1i})}{\mathrm{P}(A = \mathcal{A}_{1i} | X = X_i)} \cdot \frac{\mathrm{P}(M = M_{\mathcal{A}_{2i}} | A = \mathcal{A}_{2i}, X = X_i)}{\mathrm{P}(M = M_{\mathcal{A}_{2i}} | A = \mathcal{A}_{1i}, X = X_i)}$$

based on models:

$$\mathrm{logit}[\mathrm{P}(A = 1 | X = x)] = \gamma_0 + \gamma_1(x)$$
$$\mathrm{logit}[\mathrm{P}(M = 1 | A = a, X = x)] = \alpha_0 + \alpha_1(a) + \alpha_2(x) + \alpha_3(ax)$$

obs	$\mathcal{A}_1$	$\mathcal{A}_2$	$Y_{\mathcal{A}_1 M_{\mathcal{A}_2}}$	$M_{\mathcal{A}_2}$	X	W_1	W_2
i	1	1	y^*	m^*	x^*	$\frac{\mathrm{P}(A=1)}{\mathrm{P}(A=1\|X=x^*)}$	1
j	1	0	y^*	m^*	x^*	$\frac{\mathrm{P}(A=1)}{\mathrm{P}(A=1\|X=x^*)}$	$\frac{\mathrm{P}(M=m^*\|A=0,X=x^*)}{\mathrm{P}(M=m^*\|A=1,X=x^*)}$
k	0	0	y^{**}	m^{**}	x^{**}	$\frac{\mathrm{P}(A=0)}{\mathrm{P}(A=0\|X=x^{**})}$	1
l	0	1	y^{**}	m^{**}	x^{**}	$\frac{\mathrm{P}(A=0)}{\mathrm{P}(A=0\|X=x^{**})}$	$\frac{\mathrm{P}(M=m^{**}\|A=1,X=x^{**})}{\mathrm{P}(M=m^{**}\|A=0,X=x^{**})}$

When fitting natural effects model, account for clustering (j with i, l with k).

Modeling exposure and mediator assignment: imputation and weighting (Hong 2010; Lange, Vansteelandt, Bekaert 2012)

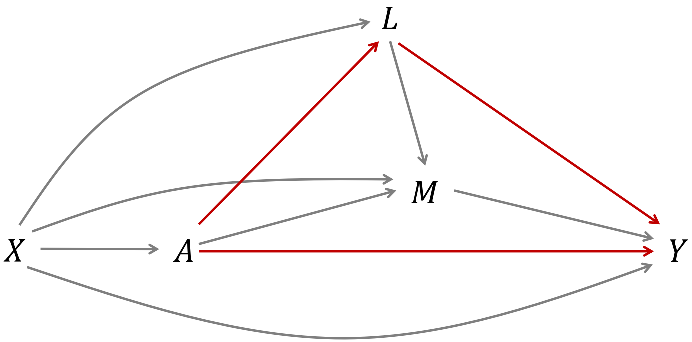
- requires the exposure and mediator models to be correctly specified
  - likely works best with binary or few-category categorical exposure/mediator
  - should check balance (Hong 2010)
- directly provides estimates for natural direct and indirect effects
  - no need to derive complex functions of data and parameters
- want to consider whether the natural effects model is correctly specified
  - covariates, interaction terms? is it incompatible w/ the other two models? (correct model is likely to be complicated!)
  - even if misspecified, if the other two models are correctly specified, is good approximation

Other variations

See

- Vansteelandt, Bekaert, Lange (2012)
- Tchetgen Tchetgen and Shpitser (2011, 2012)

Controlled direct effect
in the presence of post-exposure confounder
estimated using marginal structural model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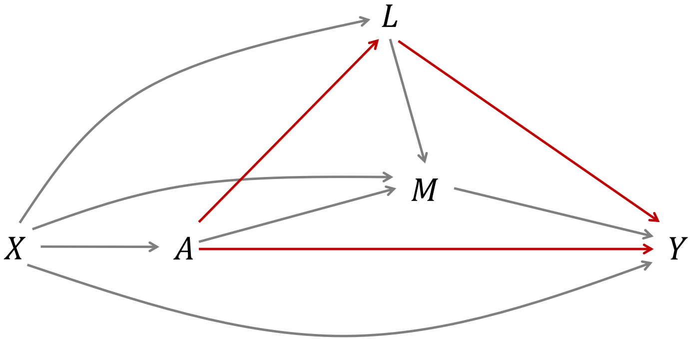


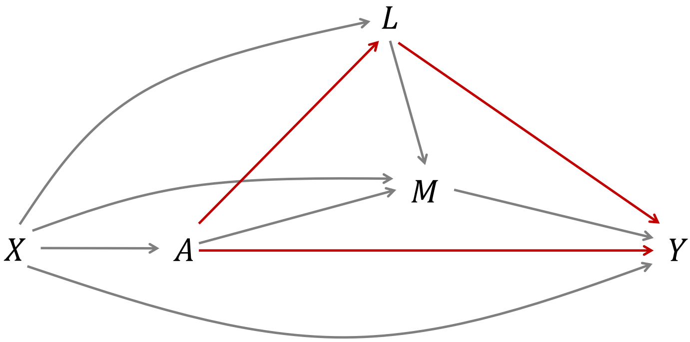
Marginal structural model (MSM) for controlled direct effect

$$E[Y_{am}] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am \Longrightarrow \text{CDE}(m) = E[Y_{1m}] - E[Y_{0m}] = (\theta_1 + \theta_3 m)(1 - 0)$$

$$\log[P(Y_{am} = 1)] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am \Longrightarrow \text{CDE}^{\text{RR}}(m) = \frac{P(Y_{1m} = 1)}{P(Y_{1m} = 1)} = e^{(\theta_1 + \theta_3 m)(1-0)}$$

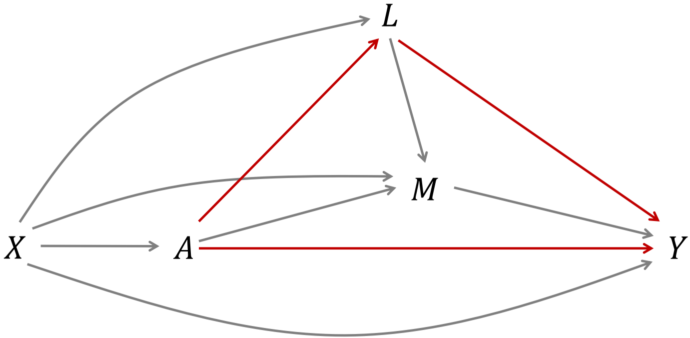
Fit MSM using weights to adjust for confounding

$$W_i = \frac{P(A = A_i)}{P(A = A_i | X = X_i)} \cdot \frac{P(M = M_i | A = A_i)}{P(M = M_i | A = A_i, X = X_i, L = L_i)}$$



Rao et al. 2015 example:

A: childhood SEC
Y: oral cancer
M: tobacco/squid/alcohol
L: adulthood SEC
X^{ALM}: paternal drinking
X^{LMY}: age, sex



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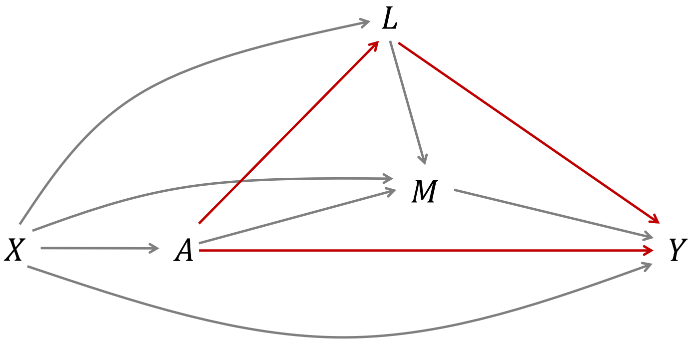
what do these models estimate?

$$\log[\mathrm{P}(Y = 1|A = a, X = x)] = \beta_0 + \beta_1 a + \beta_2 x$$

$$\log[\mathrm{P}(Y = 1|A = a, L = l, M = m, X = x)] = \beta_0 + \beta_1 a + \beta_2 l + \beta_3 m + \beta_4 x$$

$$\log[\mathrm{P}(Y_{am} = 1)] = \beta_0 + \beta_1 a + \beta_2 m \quad \text{(weighted)}$$



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$$\log[P(Y = 1|A = a, X = x)] = \beta_0 + \beta_1 a + \beta_2 x$$
$$\log[P(Y = 1|A = a, L = l, M = m, X = x)] =$$
$$\beta_0 + \beta_1 a + \beta_2 l + \beta_3 m + \beta_4 x$$
$$\log[P(Y_{am} = 1)] = \beta_0 + \beta_1 a + \beta_2 m \quad \text{(weighted)}$$

what are the weights doing?

- 1-M models
- 3-M model

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