

# Topics in Causal Inference

STAT41530

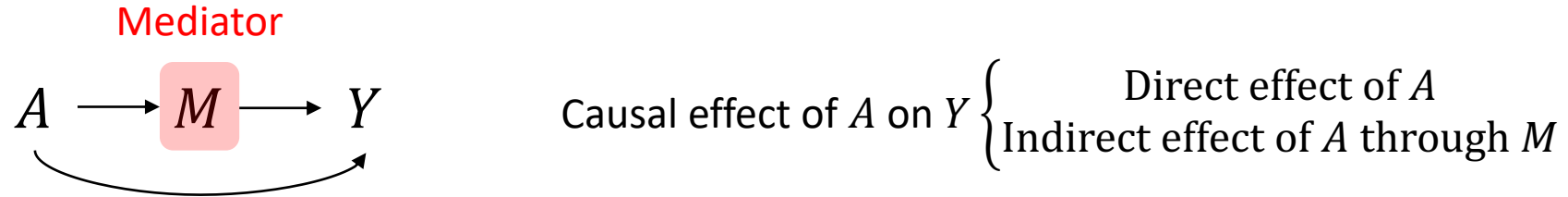
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# Lecture 8

Topic:  
Causal mediation analysis

- Traditional regression approach and examples
- Direct and indirect effects
  - Causal definitions
  - Identifiability conditions
  - Connections with the regression approach

# Mediation analysis



## Example:

$A$ : a genetic variant 15q25.1

$M$ : Smoker or not

$Y$ : lung cancer

We see associations:  $\text{Cov}(A, M) \neq 0$ ,  $\text{Cov}(A, Y) \neq 0$

Would that imply that  $M$  is a mediator for the causal effect of  $A$  on  $Y$ ?

# Motivations of mediation analysis

- Scientific understanding and explanation
  - E.g. Do genetic variants affect lung cancer through smoking or independently?
- Limiting the effects of exposure by intervening on a mediator
  - E.g. Can we eliminate the effect of antipsychotic medication on mortality by preventing the primary mechanism for mortality?
- Refinement of interventions
  - Improving components of an intervention to target mechanism
  - Eliminating costly ineffective components of an intervention
    - E.g. Does a CBT intervention improve depressive symptoms only through antidepressant use?

# Traditional regression approaches

- Estimate direct effect of  $A$

Direct effect

$$Y = \alpha_0 + \alpha_1 A + \alpha_2 M + \alpha_3 L + \varepsilon$$

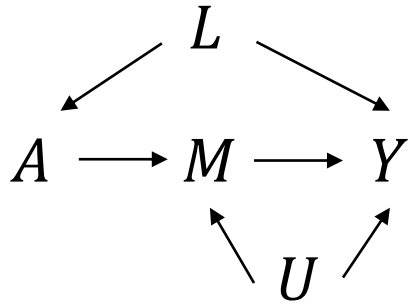
- Two ways to estimate indirect effect of  $A$

- $Y = \beta_0 + \beta_1 A + \beta_2 L + \varepsilon$  Indirect effect:  $\alpha_1 - \beta_1$

- $M = \gamma_0 + \gamma_1 A + \gamma_2 L + \varepsilon$  Indirect effect:  $\gamma_1 \alpha_2$

- When do these regressions estimate causal effect?
- Which way is correct for estimating the “indirect effect”?
- Which variables need to be included in  $L$ ?
  - **Mediator-outcome confounding:** Even if all exposure-outcome confounders are considered, there can still be confounders of mediator-outcome relationship
  - **Exposure-mediator interaction:** The linear model assumes to interaction between the exposure and mediator on the outcome

# Mediator-outcome confounding: example 1



$A$ : Smoking mother

$M$ : infant birthweight

$Y$ : infant mortality

(Yerushalmy 1972, Wilcox 1993, Hernandez-Diaz 2006)

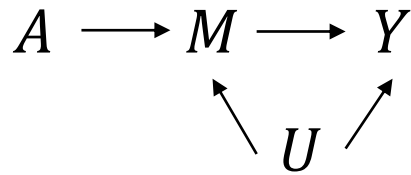
- Partition samples into birthweight stratas
- Within each strata, estimate the effect of mother smoking after controlling for confounders including mother's age, health conditions ...
- Result: for the lowest birthweight strata,  **$A$  has a positive association with  $Y$**  even after controlling for other covariates
- Does that indicate that smoking mother has a beneficial direct effect for some infants?
- **No!**

Unmeasured mediator-outcome confounder  $U$ : birth weight

Conditioning on  $M$  causes a collider bias

# Mediator-outcome confounding: example 2

SMaRT trial (Strong et. al. 2008)



$A$ : Cognitive behavioral therapy intervention (completely randomized)

$M$ : Use of antidepressant

$Y$ : Depression symptoms after 3 months

- Total causal effect of  $A$  on  $Y$ :  $\tau = E[Y(1)] - E[Y(0)]$

result:  $\tau < 0$

- Effect of  $A$  on  $M$ :  $E[M(1)] - E[M(0)] > 0$

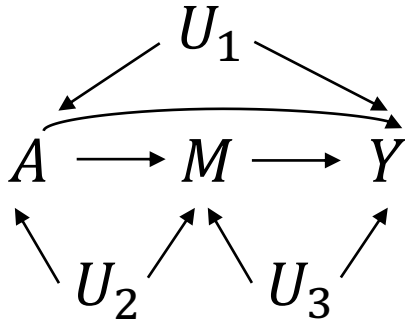
- Regress  $Y$  both on treat  $A$  and mediator  $M$ :  $Y = \alpha_0 + \alpha_1 A + \alpha_2 M + \varepsilon$

result:  $\alpha_2 > 0 !!$

Looks like Antidepressant use increases depression

- Unmeasured mediator-outcome confounder  $U$ : patient experiencing a more difficult situation

# Definitions of direct / indirect effects



$$U = (U_1, U_2, U_3)$$

Structural equation

$$Y = f(A, M, U, E_Y)$$

- Potential outcomes:

- $Y(a, m) = f(a, m, U, E_Y)$
- $Y(0), Y(1)$ :  $Y(A = 0)$  and  $Y(A = 1)$

Total effect of  $A$ :  $Y(1) - Y(0)$

- $M(0), M(1)$ : potential outcomes of  $M$  at different levels of  $A$



# Definitions of direct / indirect effects

- Direct effect of  $A$

- Controlled direct effect at  $m$

$$\begin{aligned}\text{CDE}(m) &\triangleq Y(1, m) - Y(0, m) \\ &= Y \mid do(A) = 1, do(M) = m - Y \mid do(A) = 0, do(M) = m\end{aligned}$$

Not  $Y \mid do(A), M$  !! (should not condition on a post-treatment variable)

- Natural direct effect

$$\text{NDE} = Y(1, M(0)) - Y(0, M(0))$$

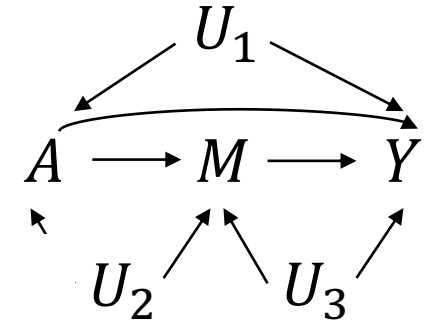
$M(0)$  can be different on different individuals

- Indirect effect of  $A$

- Natural indirect effect

$$\text{NIE} = Y(1, M(1)) - Y(1, M(0))$$

- Total effect decomposition:  $Y(1) - Y(0) = Y(1, M(1)) - Y(0, M(0)) = \text{NIE} + \text{NDE}$



# Example of the definition

	$M(0)$	$M(1)$	$Y(0,0)$	$Y(1,0)$	$Y(0,1)$	$Y(1,1)$	CDE		NDE	NIE	TE
							$m = 0$	$m = 1$			
1	0	1	0	1	0	1	1	1	1	0	1
2	1	1	0	1	0	0	1	0	0	0	0
3	0	1	0	0	0	1	0	1	0	1	1

Average NDE:  $\frac{1}{3}$

Average NIE:  $\frac{1}{3}$

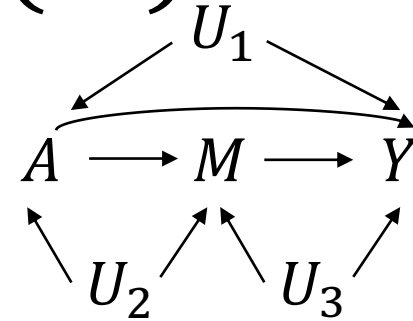
Average TE:  $\frac{2}{3} = \frac{1}{3} + \frac{1}{3}$

Average CDE(m):  $\frac{2}{3}$  for  $m = 0$  or  $1$

# Identification of average CDE( $m$ )

Need to identify  $E(Y(a, m))$

[or  $P(Y|do(A, M))$ ]



- Need to include confounders  $L$  that block all backdoor paths between  $(A, M)$  and  $Y$
- $L$  does not need to block the backdoor paths between  $A$  and  $M$

- Specifically, we need three assumptions for identifying  $E(Y(a, m))$

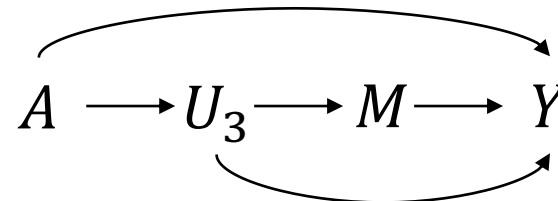
1.  $Y(a, m) \perp A \mid L$

2.  $Y(a, m) \perp M \mid A, L$

3. Positivity:  $P(M = m, A = a \mid L) > 0$

$$\begin{aligned} \mathbb{E}[Y(a, m)] &= \mathbb{E}[\mathbb{E}[Y(a, m) \mid L]] \\ &= \mathbb{E}[\mathbb{E}[Y(a, m) \mid L, A = a]] \\ &= \mathbb{E}[\mathbb{E}[Y(a, m) \mid L, A = a, M = m]] \\ &= \mathbb{E}[\mathbb{E}[Y \mid L, A = a, M = m]] \end{aligned}$$

- The first two assumptions exclude the following DAG

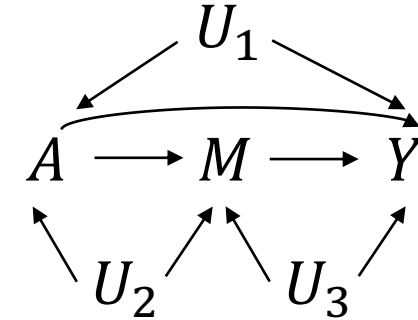


# Identification of average NDE and IDE

$$\text{NDE} = Y(1, M(0)) - Y(0, M(0))$$

$$\text{NIE} = Y(1, M(1)) - Y(1, M(0))$$

Need to identify  $E(Y(a, M(a')))$



Need three assumptions to identify  $E(Y(a, M(a')))$  (Imai et. al. 2010, Stat. Sci.)

1.  $(Y(a, m), M(a')) \perp A \mid L$  ← Much stronger than  $Y(a, m) \perp A \mid L$
2.  $Y(a, m) \perp M \mid A, L$
3. Positivity:  $P(M = m, A = a \mid L) > 0$

**Lemma:**  $(X, Y) \perp Z \Rightarrow X \perp Z \mid Y$

**Proof:**

$$\begin{aligned}
 P(X, Z \mid Y) &= \frac{P(X, Y, Z)}{P(Y)} \\
 &= \frac{P(X, Y)P(Z)}{P(Y)} = P(X \mid Y)P(Z)
 \end{aligned}$$

$$\mathbb{E}[Y(a, M(a'))] = \mathbb{E}[\mathbb{E}[Y(a, M(a')) \mid L, M(a')]]$$

$$\begin{aligned}
 &\mathbb{E}[Y(a, M(a')) \mid L, M(a') = m] \\
 &= \mathbb{E}[Y(a, m) \mid L, M(a') = m] = \mathbb{E}[Y(a, m) \mid L, M(a') = m, A = a'] \\
 &= \mathbb{E}[Y(a, m) \mid L, M = m, A = a'] = \mathbb{E}[Y(a, m) \mid L, A = a'] \\
 &= \mathbb{E}[Y(a, m) \mid L, A = a'] = \mathbb{E}[Y(a, m) \mid L] \\
 &= \mathbb{E}[Y \mid L, A = a, M = m]
 \end{aligned}$$

# Formulas for identifying direct and indirect effects

$$\begin{aligned}\mathbb{E}[Y(a, M(a')) \mid L] &= \sum_m \mathbb{E}[Y(a, m) \mid L, M(a') = m] \mathbb{P}[M(a') = m \mid L] \\ &= \sum_m \mathbb{E}[Y(a, m) \mid L, M = m, A = a] \mathbb{P}[M = m \mid L, A = a']\end{aligned}$$

- $E[\text{CDE}(m)|L] = E[Y|A = 1, M = m, L] - E[Y|A = 0, M = m, L]$
- $E[\text{NDE}|L] = \sum_m P[M = m|L, A = 0] \{E[Y|A = 1, M = m, L] - E[Y|A = 0, M = m, L]\}$
- $E[\text{NIE}|L] = \sum_m P[Y|A = 1, M = m, L] \{P[M = m|A = 1, L] - E[M = m|A = 0, L]\}$

# Connection with linear regression models

- If  $E[Y|A, M, L] = \alpha_0 + \alpha_1 A + \alpha_2 M + \alpha_3 L$
- Then  $\alpha_1 = E[\text{CDE}(m)|L] = E[\text{NDE}|L]$  direct effect

- What about indirect effect  $E[\text{NIE}|L]$  ?

- If we assume  $E[Y|A, L] = \beta_0 + \beta_1 A + \beta_2 L$

Then  $E[Y(1) - Y(0)|L] = E[Y|A = 1, L] - E[Y|A = 0, L] = \beta_1$

$E[\text{NIE}|L] = \alpha_1 - \beta_1$  (total effect decomposition)

- If we assume  $E[M|A, L] = \gamma_0 + \gamma_1 A + \gamma_2 L$

$$\begin{aligned}\mathbb{E}[\text{NIE} | L] &= \sum_m \mathbb{E}[Y | A = 1, M = m, L] (\mathbb{P}[M = m | A = 1, L] - \mathbb{P}[M = m | A = 0, L]) \\ &= \sum_m (\alpha_0 + \alpha_1 + \alpha_2 m + \alpha_3 L) (\mathbb{P}[M = m | A = 1, L] - \mathbb{P}[M = m | A = 0, L]) \\ &= \alpha_2 \sum_m m (\mathbb{P}[M = m | A = 1, L] - \mathbb{P}[M = m | A = 0, L]) \\ &= \alpha_2 (\mathbb{E}[M | A = 1, L] - \mathbb{E}[M | A = 0, L]) = \alpha_2 \beta_1\end{aligned}$$