DECART Summer School 2018:

Causal Inference Module

Mediation Analysis

Mediation and Moderation

- **Effect Moderation**:

In whom does the treatment affect the outcome, or more generally, what is the effect of the treatment on the outcome in different subgroups

  - Key pragmatic goal is to define which patients will benefit the most from a treatment (or be harmed the most by an exposure)

  - Can also provide insights regarding mechanism

Effect Moderation Example

- If we have a treatment (e.g. certain medication) Ai, with 1 being where the patient is given the medication and 0 not.
- The outcome of interest Y_i is some continuous measure (e.g. certain serum biomarker level, with higher the better).
- If age (X_i) turns out to be an effect modifier, such that we have a regression model

  $$Y_i = 10 + 2 * X_i + 10 * A_i - 0.2 * X_i * A_i + \varepsilon_i$$

- For subject i with of age $X_i = x$,

  if $A_i = 1$ then $Y_i = 10 + 2x + 10 - 0.2x + \varepsilon_i$

  if $A_i = 0$ then $Y_i = 10 + 2x + \quad\quad\quad\quad + \varepsilon_i$

  the treatment effect is then $\Delta Y = 10 - 0.2x = 0.2 * (50 - x)$

Effect Moderation Example

- The treatment effect $\Delta Y = 10 - 0.2x = 0.2 * (50 - x)$
  for $x < 50$, $\Delta Y > 0$ (treatment is beneficial)
  for $x \geq 50$, $\Delta Y \leq 0$ (maybe harmful)

- We can thus personalize the mediation to the group who can actually benefit from it (e.g. patients younger than 50)

- In general, if $\boldsymbol{X_i} = (X_{i1}, X_{i2}, \ldots, X_{ip})$ is a vector of multiple patient (pretreatment) characteristics (e.g. age, gender, BMI,…), the treatment effect is then a function of all these effect modifiers ΔY=g$(X_{i1}, X_{i2}, \ldots, X_{ip})$.

- For a given patient, the value $(X_{i1}, X_{i2}, \ldots, X_{ip}) = (x_1, x_2, \ldots, x_p)$ is known before treatment assignment.

- A good **personalized treatment regime** would be to assign the treatment to patient whose g$(x_1, x_2, \ldots, x_p)$>0 (benefitial).

Mediation and Moderation

- **Mediation:** Addresses *how* a treatment affects the outcome
  - Mechanisms or pathways by which a treatment affects outcome
  - Goals:

    a) scientific explanation and understanding

    b) refining an intervention by discarding ineffective components of the intervention and focusing on effective components

    c) evaluating the extent to which a detrimental effect of an exposure on an outcome can be blocked by intervening on the mediator

Mediation Example

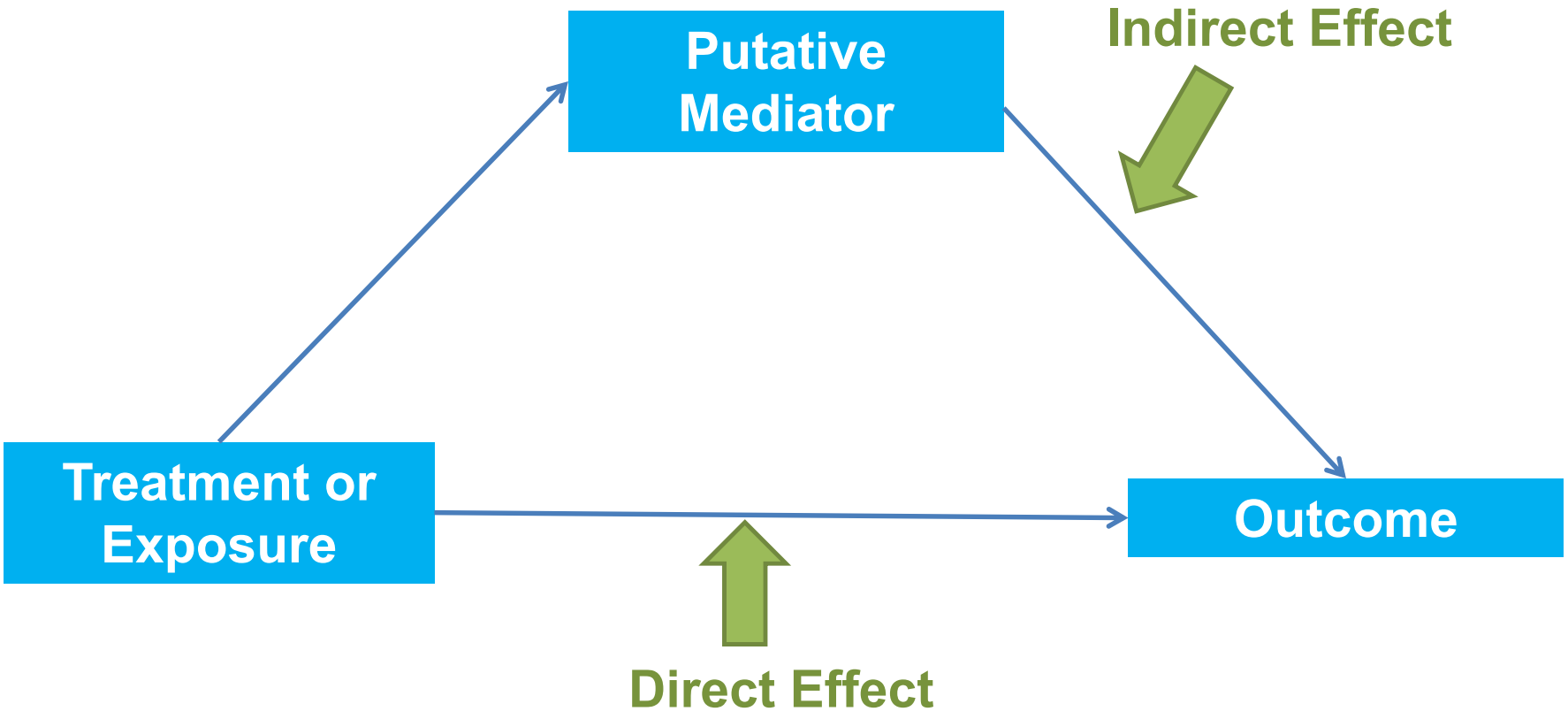
- Again consider we have a treatment A_i for subject i and an (continuous) outcome Y_i.
- Consider a mediator M_i which is a pathway that mediates the effect of A on Y.
- If you change A_i from 0 to 1, Y_i would change from 10 to 20, the overall effect of A on Y is thus $\Delta Y = 10$.
- If you first somehow fix the value of M_i while change A_i from 0 to 1, then Y_i change from 10 to 15 ($\Delta Y' = 5$).
- If there is no unobserved confounding effect, then we can conclude that the difference $\Delta Y - \Delta Y' = 5$ is the effect of A on Y that mediated through M.
-
- M thus mediates $\frac{\Delta Y - \Delta Y'}{\Delta Y} = \frac{5}{10} = 50\%$ of the overall effect.

Examples of Questions Addressed by Mediation Analysis

- A genetic variation has been shown to be associated both with smoking behavior and with lung cancer.
  - Do the variants affect lung cancer only because they affect smoking behavior, or do the variants affect lung cancer in part by other pathways not related to smoking?

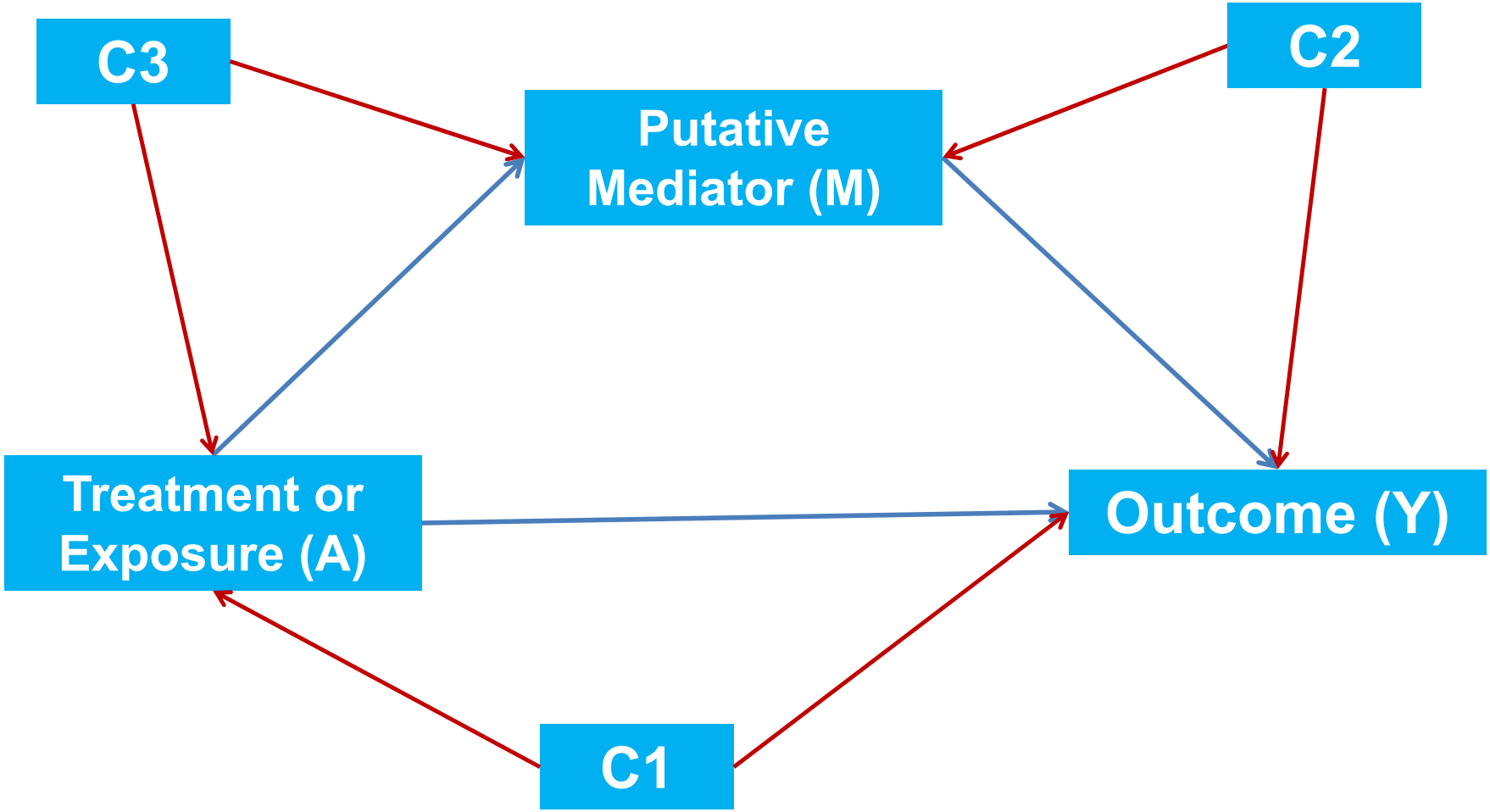
- Low SES during childhood is associated with both low SES later in life and with adverse health outcomes later in life.
  - Does low childhood SES affect later health outcomes only because it affects SES later in life which in turn affects later health outcomes, or does childhood SES affect adult health outcomes through other pathways, not related to adult SES, or some combination of both?

DAG for Simple Mediation Analysis

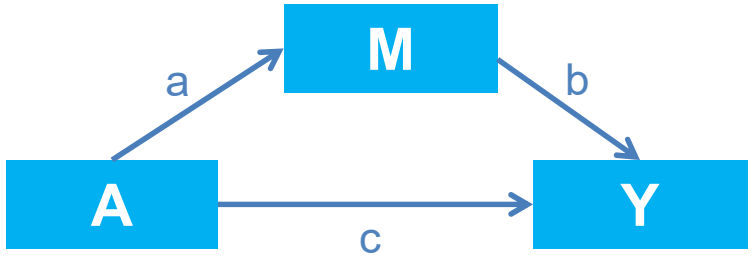


What is missing from this DAG?

DAG for Simple Mediation Analysis



Standard Approach: Product Method



- A = treatment or exposure
- M = mediator
- Y = outcome

> Product Method (Baron and Kenny, 1986)

regress M on A: $E[M|A=a, C=c] = \beta_0 + \beta_1 a + \beta_2' c$

regress Y on M and A: $E[Y|A=a, M=m, C=c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3' c$

The direct effect is θ_1

The indirect effect is $\tau = \beta_1 \theta_2$

For statistical inference: the most popular estimator for variance is the Sobel's estimator (Sobel 1982)

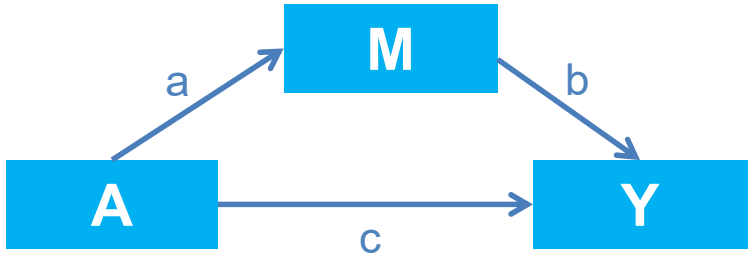
$$var(\hat{\tau}) = \hat{\beta}_1^2 s_{\theta_2}^2 + \hat{\theta}_2^2 s_{\beta_1}^2$$

which is derived from multivariate delta method, s_{θ_2} and s_{β_1} are the standard errors.

May also use this to do hypothesis testing on whether the indirect effect is 0 (Sobel's test).

Standard Approach: Difference Method

- A = treatment or exposure
- M = mediator
- Y = outcome



> Difference Method

regress Y on A: $E[Y|A=a, C=c] = \phi_0 + \phi_1 a + \phi_2' c$

regress Y on M and A: $E[Y|A=a, M=m, C=c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3' c$

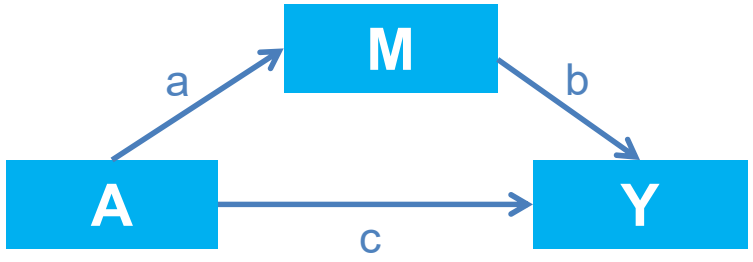
The direct effect is θ_1

The indirect effect is $\tau = \phi_1 - \theta_1$

For continuous outcome, the product method and difference method will coincide (assuming the models are correctly specified, see MacKinnon et al., 1995)

Standard Approach: Joint Significant Test

- If the primary interest is testing whether the indirect effect exists $H_0: \tau = 0$
  (not effect size estimation)



> Joint significant test (MaxP test) is also commonly used

regress M on A: $E[M|A = a, C = c] = \beta_0 + \beta_1 a + \beta_2' c$

regress Y on M and A: $E[Y|A = a, M = m, C = c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3' c$

Test for path a: $T_a = \frac{\hat{\beta}_1}{s_{\beta_1}} \sim N(0,1) \Rightarrow$ p-value p_a

Test for path a: $T_b = \frac{\hat{\theta}_2}{s_{\theta_2}} \sim N(0,1) \Rightarrow$ p-value p_b

Test for $H_0: \tau = 0$ is then $p_\tau = \max(p_a, p_b)$

Thus it is significant ($p_\tau < 0.05$) only when both A-M association ($p_a < 0.05$) and M-Y association ($p_b < 0.05$) are significant.

Counterfactual Framework for Mediation Analysis

- A = treatment or exposure
- M = putative mediator
- Y = outcome
- Let Y(a,m) denote the potential outcome for Y if A is set to a and M is set to M
- Let M(a) denote the potential outcome for M if A is set to a

- Note: here we have different counterfactuals defined here

  before is Y(0) and Y(1)

  but now Y(0,M(0)) = Y(0), Y(1,M(1)) = Y(1), and we have more, for example Y(0,M(1)), Y(1,M(0))
- Same amount of information, but more unknown

  → more identifiability assumptions !!

Counterfactual Notation and Framework

- The *controlled direct effect (CDE)* represents the effect of changing A from a* to a on Y while intervening to fix M at a fixed value m. The individual controlled direct effect of changing A to a from a* at m is:

  $$CDE(m) = Y(a,m) - Y(a^*,m)$$

- The average CDE in the population is $E[Y(a,m) - Y(a^*,m)]$
- The average CDE conditional on covariates C = c is $E[Y(a,m) - Y(a^*,m) \mid c]$
- The natural direct effect (NDE) represents the effect of changing A from a* to a on Y while intervening to fix M at the value M(a*) that M would have had if A had been a*. The natural direct effect is defined as:

  $$NDE = Y(a,M(a^*)) - Y(a^*,M(a^*))$$

- The average NDE in the population is $E[Y(a,M(a^*)) - Y(a^*,M(a^*))]$
- The average NDE conditional on covariates C = c is

  $$E[Y(a,M(a^*)) - Y(a^*,M(a^*)) \mid c]$$

Counterfactual Notation and Framework

- The *natural indirect effect (NIE)* represents the effect of comparing fixing the mediator to M(a) vs. M(a*) while intervening to set the exposure to A = a. The individual NIE is defined as:

  $NIE = Y(a, M(a)) - Y(a, M(a^*))$

- A non-zero NIE requires first that the exposure affects the mediator, and then that changing the mediator in turn affects the outcome.
- The average NIE in the population is:

  $E[Y(a,M(a)) - Y(a, M(a^*))]$

- The average NIE conditional on covariates C = c is

  $E[Y(a,M(a)) - Y(a, M(a^*)) \mid c]$

Decomposition of Total Effect

- Total Effect = $Y(a,M(a)) - Y(a^*,M(a^*))$

$=[Y(a,M(a)) - Y(a,M(a^*))] + [Y(a,M(a^*) - Y(a^*,M(a^*))]$

Natural Indirect effect

Natural Direct effect

- Corresponding decompositions for population average and conditional average versions of these effects

Assumptions for Effect Estimates to Have Causal Interpretation

To estimate the controlled direct effect:

A1) No unmeasured confounding for exposure-outcome relationship

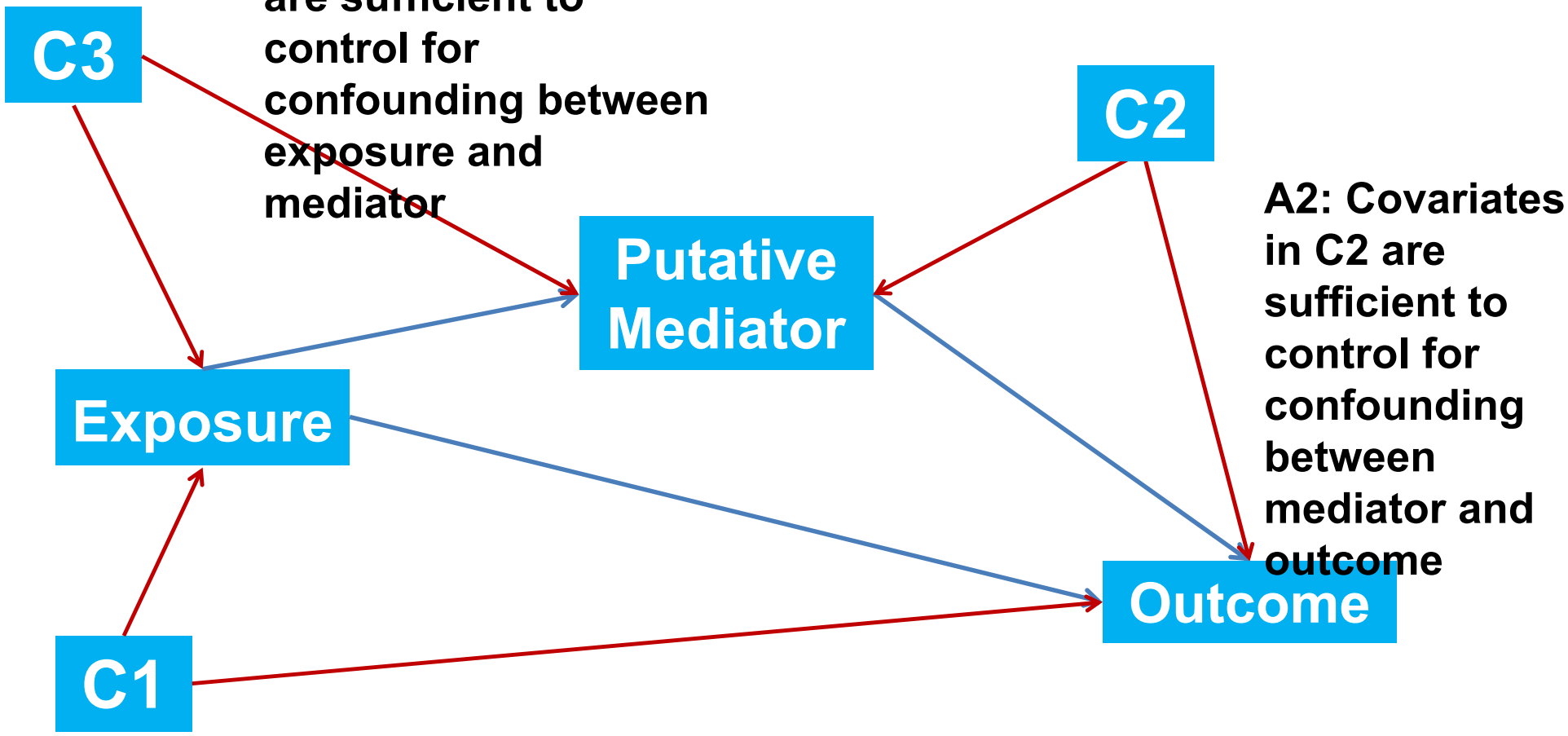
A2) No unmeasured confounding for mediator-outcome relationship

To estimate natural direct and indirect effects:

A3) No unmeasured confounding for exposure-mediator relationship

A4) No confounder of the mediator-outcome relationship is affected by the exposure

DAG for Simple Mediation Analysis



A1: Covariates in C1 are sufficient to control for confounding between exposure and outcome

No-Confounding Assumptions to Estimate Causal Effects

Type of Effect	RCT	Observational Study
Natural Direct and Indirect Effects	A2, A4	A1, A2, A3, A4
Controlled Direct Effect	A2	A1, A2
Total Effect	None	A1 Only

A1) No unmeasured confounding for exposure-outcome relationship
$Y(a,m) \perp A|C$

A2) No unmeasured confounding for mediator-outcome relationship
$Y(a,m) \perp M|C,A$

A3) No unmeasured confounding for exposure-mediator relationship
$\mathrm{M}(a) \perp A|C$

A4) No confounder of the mediator-outcome relationship is affected by the exposure, $\mathrm{Y}(a,m) \perp M(a^*)|C$

Design Considerations

- Usually, mediation assumptions are best justified if:
  - Baseline levels of mediator and outcome are obtained, and either controlled for as covariates or used so that the mediator and outcome are expressed as pre-post differences
  - Measurements of exposure, mediator and outcome follow the temporal order:

    exposure -> mediator -> outcome
  - The mediator is assessd relatively soon after the occurrence of the exposure, and well before the outcome

Non-Parametric Causal Effect Estimates

If A1-A4 hold, then

$$E[Y(a,m) - Y(a^*,m)|c] = E[Y|a,m,c] - E[Y|a^*,m,c]$$

$$E[Y(a,M(a^*)) - Y(a^*,M(a^*))|c] = \Sigma_m \{E[Y|a,m,c] - E[Y|a^*,m,c]\} Pr(m|a^*,c)$$

$$E[Y(a,M(a)) - Y(a,M(a^*))|c] = \Sigma_m E[Y|a,m,c] \{Pr(m|a,c) - Pr(m|a^*,c)\}$$

- The LHS for each equation are the counterfactual quantities that define the controlled direct effect, natural direct effect, and natural indirect effects, respectively.
- The RHS for each equation are estimable from the data.
- The top expression for the CDE requires only A1 and A2; the latter two expressions require A1, A2, A3 and A4.

Mediation Analysis with Linear Models
(Continuous Outcomes and Continuous Mediators)

No Interaction Model:

$$E(M|A=a,C=c) = \beta_0 + \beta_1 a + \beta_2 c$$

$$E(Y|A=a,M=m,C=c) = \theta_0 + \theta_1 a + \theta_2 m + \theta_4 c$$

$$CDE(m) = \theta_1 (a - a^*)$$

$$NDE = \theta_1 (a - a^*)$$

$$NIE = \beta_1 \theta_2 (a - a^*)$$

essentially the product method

Mediation Analysis with Linear Models
(Continuous Outcomes and Continuous Mediators)

Interaction Model:

$$E(M|A=a,C=c) = \beta_0 + \beta_1 a + \beta_2 c$$

$$E(Y|A=a,M=m,C=c) = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 a \cdot m + \theta_4 c$$

$$CDE(m) = (\theta_1 + \theta_3 m)(a - a^*)$$

$$NDE = (\theta_1 + \theta_3 \cdot [\beta_0 + \beta_1 a^* + \beta_2 c])(a - a^*)$$

$$NIE = (\beta_1 \theta_2 + \beta_1 \theta_3 a)(a - a^*)$$

Can assess the standard errors through delta method (similar as in Sobel's estimator) or bootstrap

Mediation Analysis with Continuous Mediator and Binary Outcome

$M = \beta_0 + \beta_1 a + \beta_2 c + \varepsilon_m$, with $\varepsilon_m \sim N(0, \sigma^2)$

$\text{logit}[Pr(Y=1)|A=a,M=m,C=c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 a \cdot m + \theta_4 c$

> For rare outcome (rule of thumb: prevalence ≤ 10%)

$\log\{OR^{CDE}(m)\} = (\theta_1 + \theta_3 m)(a - a^*)$

$\log\{OR^{NDE}\} = [\theta_1 + \theta_3 \cdot (\beta_0 + \beta_1 a^* + \beta_2' c + \theta_2 \sigma^2)](a - a^*)$
$+ 0.5 \cdot \theta_3^2 \sigma^2 (a^2 - a^{*2})$

$\log\{OR^{NIE}\} = (\beta_1 \theta_2 + \beta_1 \theta_3 a)(a - a^*)$

> If the outcome is not rare (prevalence > 10%)
use log-linear regression model for the outcome

Standard errors using delta method or bootstrap

Mediation Analysis with Continuous Mediator and Count Outcome

$M = \beta_0 + \beta_1 a + \beta_2 c + \varepsilon_m$, with $\varepsilon_m \sim N(0, \sigma^2)$

$E(Y|A=a,M=m,C=c) = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 a \cdot m + \theta_4 c$

Y ~ Poisson or negative binomial

$\log\{RR^{CDE}(m)\} = (\theta_1 + \theta_3 m)(a - a^*)$

$\log\{RR^{NDE}\} = [\theta_1 + \theta_3 \cdot (\beta_0 + \beta_1 a^* + \beta_2 c + \theta_2 \sigma^2)](a - a^*)$
$+ 0.5 \cdot \theta_3^2 \sigma^2 (a^2 - a^{*2})$

$\log\{RR^{NIE}\} = (\beta_1 \theta_2 + \beta_1 \theta_3 a)(a - a^*)$

Normality assumption most important if the interaction is substantial

Mediation Analysis with Continuous Outcome and Binary Mediator

$$\text{logit}\{\Pr(M=1|A=a,C=c)\} = \beta_0 + \beta_1 a + \beta_2 c$$

$$E(Y|A=a,M=m,C=c) = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 a \cdot m + \theta_4 c$$

We have

$$CDE(m) = (\theta_1 + \theta_3 m)(a - a^*)$$

$$NDE = \theta_1 (a - a^*) + \theta_3 (a - a^*) \frac{\exp\{\beta_0 + \beta_1 a^* + \beta_2' c\}}{1 + \exp\{\beta_0 + \beta_1 a^* + \beta_2' c\}}$$

$$NIE = (\theta_2 + \theta_3 a) \left\{ \frac{\exp\{\beta_0 + \beta_1 a + \beta_2' c\}}{1 + \exp\{\beta_0 + \beta_1 a + \beta_2' c\}} - \frac{\exp\{\beta_0 + \beta_1 a^* + \beta_2' c\}}{1 + \exp\{\beta_0 + \beta_1 a^* + \beta_2' c\}} \right\}$$

Software Package for Mediation Analysis (with Causal Inference Perspective)

- SAS (PROC CAUSALMED, also see Valeri and VanderWeele, 2013)
- SPSS (Valeri and VanderWeele, 2013)
- Stata (command is ‘paramed’)
- R package {mediation}
- Also see http://davidakenny.net/cm/mediate.htm (for other perspectives)

Sensitivity Analysis

- Suppose we wish to estimate the effect of changing A from a* to a on a binary outcome variable Y
- Assume analysis of Y is on risk ratio scale (or odds ratio if prevalence of Y is ≤ 0.10 or so)
- Let γ = the effect of dichotomous unmeasured U on Y conditional on A and C expressed as a risk ratio:

$$\gamma = \frac{\Pr(Y=1|a,c,\ U=1)}{\Pr(Y=1|a,c,\ U=0)}$$

- $B_{mult}(c) = \frac{1+(\gamma-1)\Pr(U=1|a,c)}{1+(\gamma-1)\Pr(U=1|a*,c)}$
- Estimate causal effect of A on Y as

$$\hat{\beta}/B_{mult}(c)$$

- Vary γ, $\Pr(U=1|a,c)$ and $\Pr(U=1|a*,c)$ over range of plausible values to perform sensitivity analysis

Multiple Mediators

- Suppose the confounding assumptions A1-A4 hold for the vector of mediators **M** = $(M^{(1)}, \ldots, M^{(K)})$ and the **M** and Y are continuous variables that satisfy:

$$E[Y|a,\mathbf{m},c] = \theta_0 + \theta_1 + \theta_2^{(1)} m^{(1)} + \theta_2^{(2)} m^{(2)} + \ldots + \theta_2^{(K)} m^{(K)} + \theta_4 c$$

$$E[M^{(i)}|a,c] = \beta_0^{(i)} + \beta_1^{(i)} a + \beta_2^{(i)} c,\ i = 1, 2, \ldots, K.$$

Then overall CDE, NDE, and NIE's are given by:

$$CDE(m) = \theta_1(a - a^*)$$

$$NDE = \theta_1(a - a^*)$$

$$NIE = [\beta_1^{(1)} \theta_2^{(1)} + \beta_1^{(2)} \theta_2^{(2)} + \beta_1^{(K)} \theta_2^{(K)}](a - a^*)$$

- **Note (1):** If there is a confounder C* of a mediator and outcome which is influenced by the treatment, this can be addressed in the multiple mediator framework by adding the confounder to the list of mediators **M**.
- **Note (2):** On the other hand, Assumptions A1-A4 must now hold for K different mediators, which is harder to justify than that Assumptions A1-A4 hold for a single mediator.

Multiple Mediators

- Suppose the confounding assumptions A1-A4 hold for the vector of mediators **M** = ($M^{(1)}$, …, $M^{(K)}$) and the **M** and Y are continuous variables that satisfy:

$$E[Y|a,\mathbf{m},c] = \theta_0 + \theta_1 + \theta_2^{(1)} m^{(1)} + \theta_2^{(2)} m^{(2)} + \ldots + \theta_2^{(K)} m^{(K)} + \theta_4 c$$

$$E[M^{(i)}|a,c] = \beta_0^{(i)} + \beta_1^{(i)} a + \beta_2^{(i)} c,\ i = 1, 2, \ldots, K.$$

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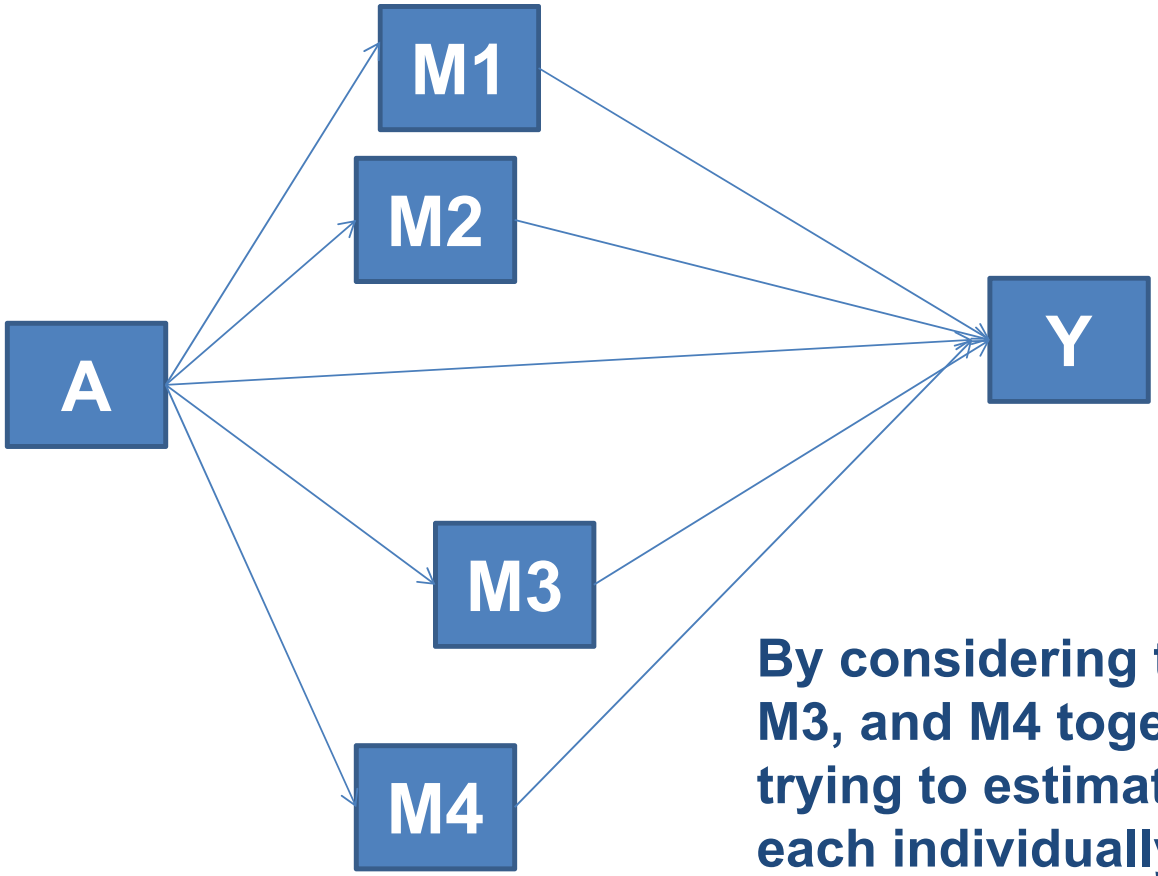
$$NIE = [\beta_1^{(1)} \theta_2^{(1)} + \beta_1^{(2)} \theta_2^{(2)} + \beta_1^{(K)} \theta_2^{(K)}](a - a^*)$$

Note (3): If there is a multiplicative linear interaction between a and $M^{(i)}$ given by addition of $\theta_3^{(i)} m^{(i)}$ on the RHS of E[Y|a,**m**,c], then add $\theta_3^{(i)} m^{(i)}$ (a – a*) to the CDE, $\theta_3^{(i)}[\beta_0^{(i)} + \beta_1^{(i)} a^* + \beta_2^{(i)} c]$ (a – a*) to the NDE, and $\theta_3^{(i)} \beta_1^{(i)}$ a(a-a*) to the NIE.

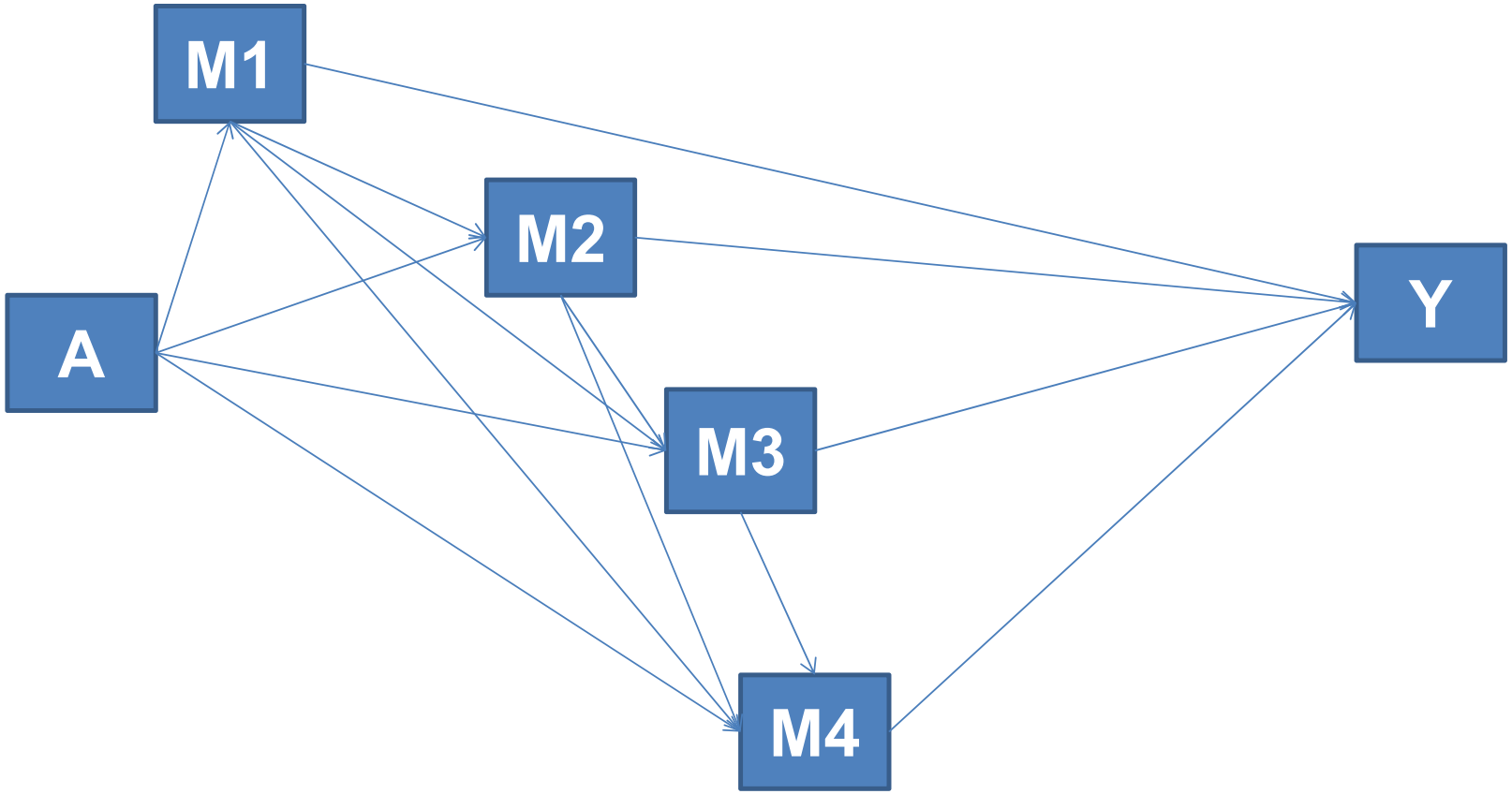
Multiple Mediators

- This approach to mediation analysis does not attempt to estimate indirect effects which are specific to each mediator.
- This avoids the need to make difficult (usually untenable) assumptions about the causal effects of each mediator on the other.



**By considering the indirect effect of M1, M
M3, and M4 together, rather than
trying to estimate indirect effects through
each individually, we do not have to articu
directions of causal effects among the Ms**

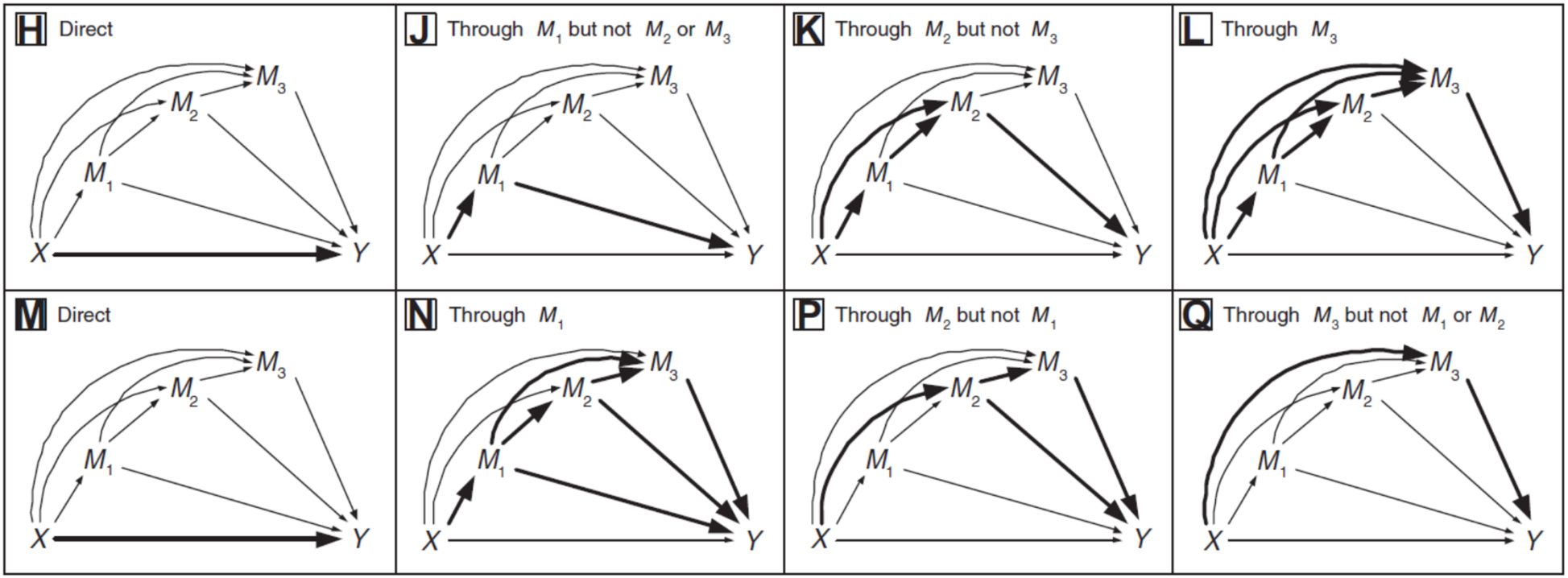
Multiple Mediators



- If causal ordering among M1, M2, …., MK is known, we can carry out a sequence of separate mediation analyses to first estimate direct and indirect effects mediated through M1; then to estimate direct and indirect effects mediated through M1 and M2, and so on.

Mediator-Specific Effects for Multiple Mediators

An illustration of the two possible ways of defining mediator-specific natural effects through three mediators.



Adapted from Daniel et al. 2015. *Biometrics*, *71*(1), 1-14.