Mediation analyses

Advanced Psychometrics Methods in Cognitive Aging Research Workshop

June 6, 2016

Goals for today

- Motivate mediation analysis
- Survey rapidly developing field in epidemiology
- Provide two easy Stata tools for analysis, with guidance on assumptions, set-up, and interpretation of results
    - SAS and SPSS macros by Valeri and VanderWeele using slightly different approach are available but not covered

Motivation for studying mediation

- Mediation analysis assesses causal effects of exposure on outcome that operate through intermediates
- Like confounding, mediation is inherently a causal concept
- Two sorts of questions addressed by mediation analysis:
  1. What is the potential effect of an intervention on both mediator and outcome?
  2. What is the mechanism linking exposure to outcome, and what part of its effect is due to effects on the mediator?

Examples of mediation problems

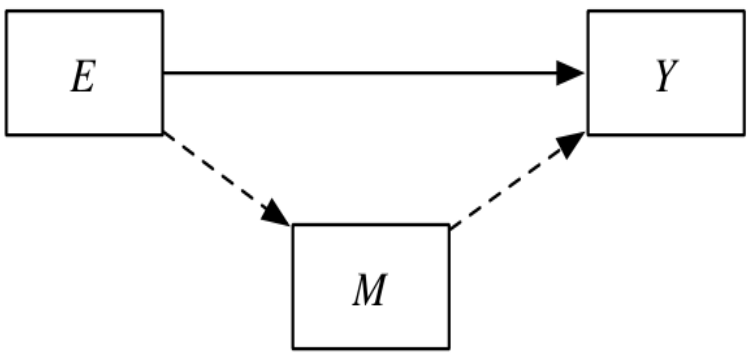
- What causal pathways link depression to cognitive decline? Is it lack of exercise, smoking, alcohol use or something else?
- Why was the MIRA trial of diaphragm use to prevent male-to-female HIV transmission negative? Do diaphragms not reduce transmission of HIV, or did diaphragm use lead to decreased condom use?
- Is change in bone mineral density (BMD) an adequate surrogate outcome for RCTs of drugs for fracture prevention? That is, does BMD mediate almost all of the treatment effect on fracture?

Motivation for causal approaches to mediation

- Traditional approach has hidden assumptions, limitations
- Consider an exposure E, an outcome Y and mediator M
- Even when E is randomized, the relationship between M and Y may be confounded
- Also, traditional methods
  - do not allow for $E - M$ interaction
  - potentially biased with binary, survival outcomes
  - do not properly account for *causal intermediates*
- Causal methods clarify required assumptions, address these difficulties, and are easily implemented in Stata

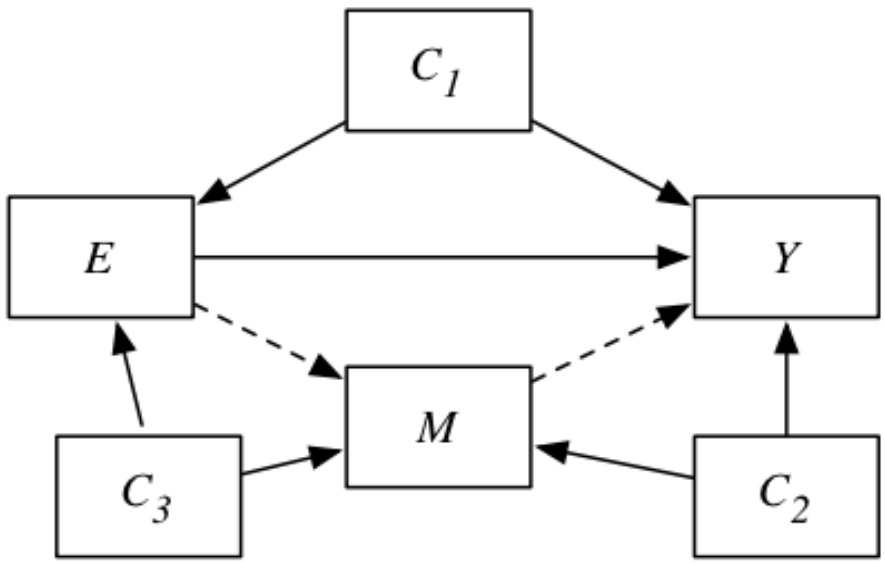
Traditional Baron and Kenny approach

- Mediation of effect of exposure E on outcome Y by mediator M
- *Total effect* of E on Y can be decomposed into
  - *direct effect* (solid line)
  - *indirect effect* (dashed lines)



Traditional Baron and Kenny approach

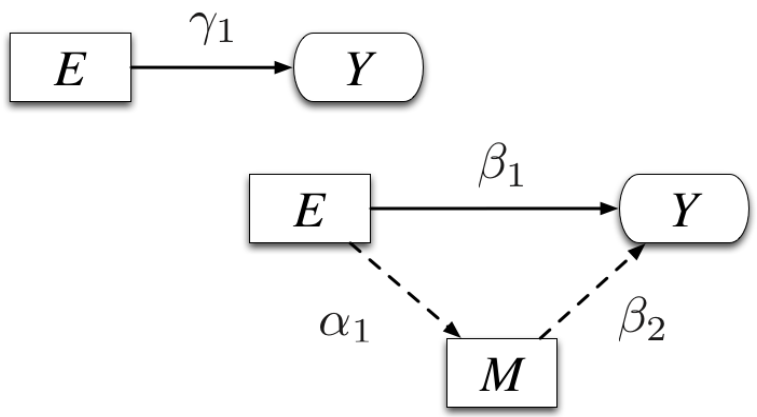
- Assess mediation by showing that
  - $E \rightarrow M$, adjusting for C_3
  - $M \rightarrow Y$, adjusting for E, C_1, and C_2
  - adjustment for M attenuates estimate of $E \rightarrow Y$



Traditional Baron and Kenny approach

- With continuous M and Y, we assume

$$\begin{aligned} \mathrm{E}[Y|E,C_1] &= \gamma_0 + \gamma_1 E + \gamma_2 C_1 && (1) \\ \mathrm{E}[M|E,C_3] &= \alpha_0 + \alpha_1 E + \alpha_2 C_3 && (2) \\ \mathrm{E}[Y|E,M,C_1,C_2] &= \beta_0 + \beta_1 E + \beta_2 M + \beta_3 C_1 + \beta_4 C_2 && (3) \end{aligned}$$



- total effect $= \gamma_1$
- direct effect $= \beta_1$
- indirect effect $= \gamma_1 - \beta_1 = \alpha_1\beta_2$

Traditional Baron and Kenny approach - drawbacks

- Does not accommodate interaction of E and M
- Crucial to control for $M \rightarrow Y$ confounding
  - special methods needed if $M \rightarrow Y$ confounder is a *causal intermediate* (more later)
- With logistic, Cox models:
  - difference between γ_1 and β_1 may be partly explained by *non-collapsibility*
  - $\gamma_1 - \beta_1$ or $\exp(\gamma_1) - \exp(\beta_1)$ hard to interpret as indirect effects (also true of Poisson, negative binomial models)

Proportion of treatment effect explained (PTE)

- Usually calculated on coefficient scale in logistic, Poisson, Cox models

$$PTE = \frac{\gamma_1 - \beta_1}{\gamma_1}$$

- Drawbacks:
  - may not behave like a proper proportion
    - $PTE < 0$ if $|\beta_1| > |\gamma_1|$ and both have same sign (i.e., negative mediation)
    - $PTE > 1$ if γ_1 and β_1 have opposite signs (e.g., adverse indirect and overall effects, beneficial direct effect)
  - Confidence intervals often wide, also hard to calculate
    - $\gamma_1,\ \beta_1$ estimated using same data, different models
    - bootstrapping is an option

Mediation - causal view

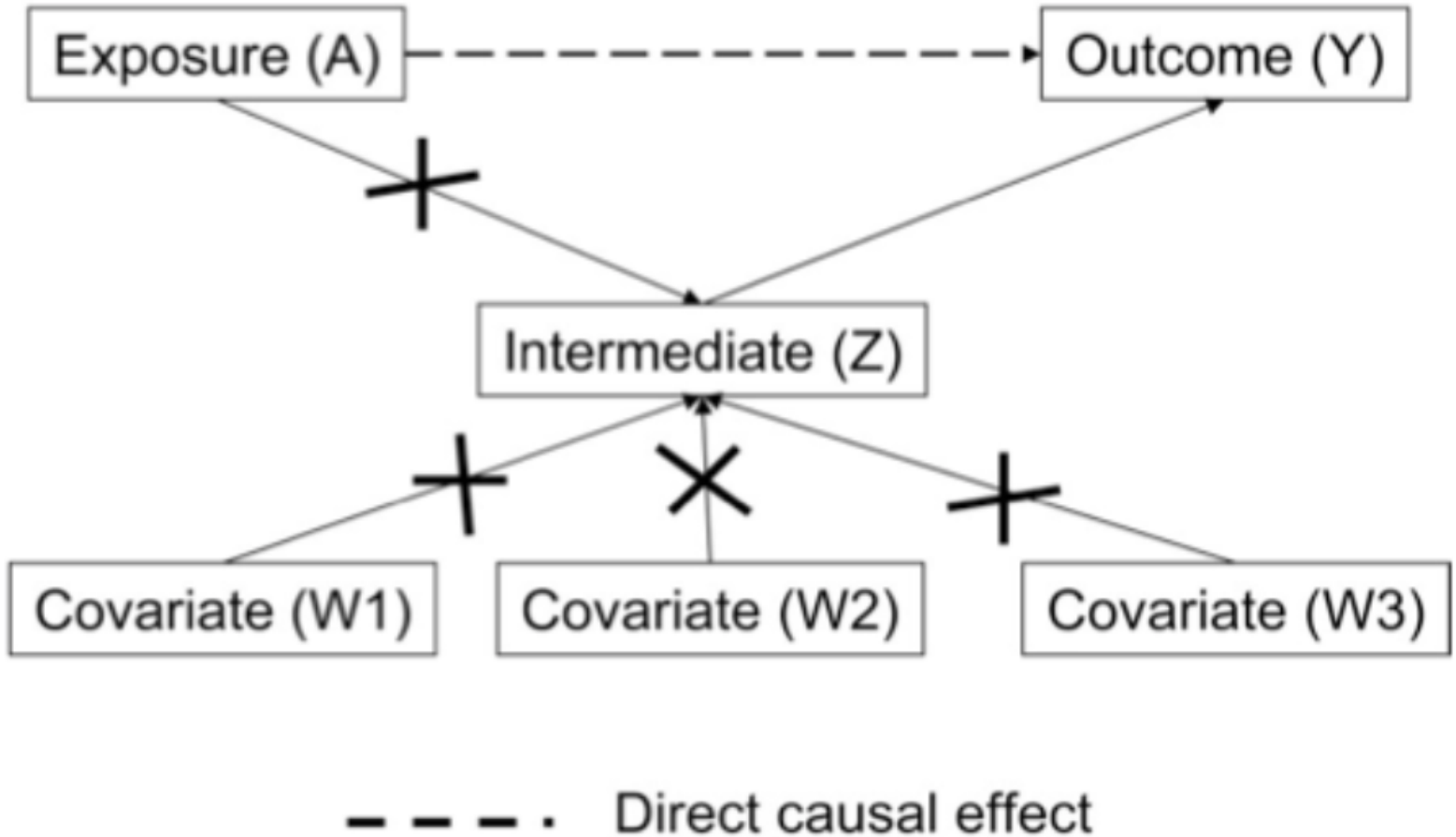
- Causal definitions of direct and indirect effects are based on averages of potential outcomes indexed by both the exposure and the mediator: $Y(e, m)$
- $Y(e, m)$: potential outcome with E set to e, M set to m
- Five causal effect measures for mediation
  - controlled direct effect
  - pure and total natural direct effects
  - total and pure natural indirect effects
- In some cases, these will collapse to Baron and Kenny's direct and indirect effects

- The *controlled direct effect (CDE)* is the average causal effect of exposure when the mediator M is set to m for everyone
- Controlled direct effect, with binary E, setting $M = m$:

$$\mathsf{E}[Y(1, m)] - \mathsf{E}[Y(0, m)]$$

- With binary Y, this CDE is a risk difference
- Interpretable as effect of E when all natural influences on M are blocked (intervention sets it)

CDE: all natural influences on mediator blocked



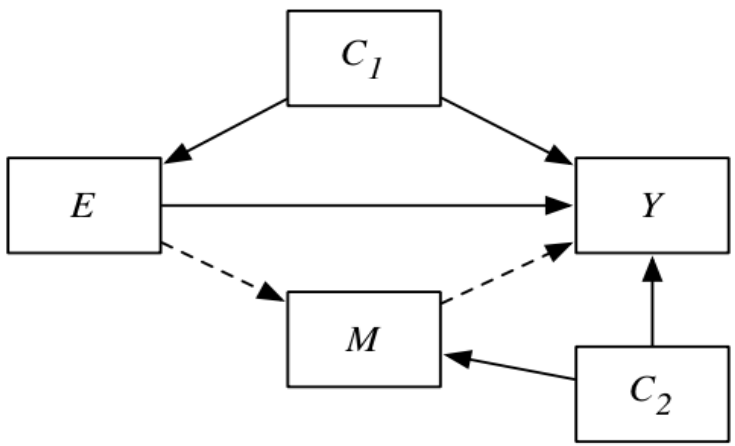
Petersen *et al.*, *Epidemiology*, 2006;17:276-84.

CDEs potentially estimable in an RCT

- Treatment with beneficial and adverse effects
  1. hormone therapy has beneficial effects on lipids, vascular reactivity, but is thrombogenic
  2. diaphragm in MIRA trial may have directly reduced HIV transmission, but it also decreased condom use
- CDE could be estimated in RCT of a joint intervention that blocks the adverse pathway

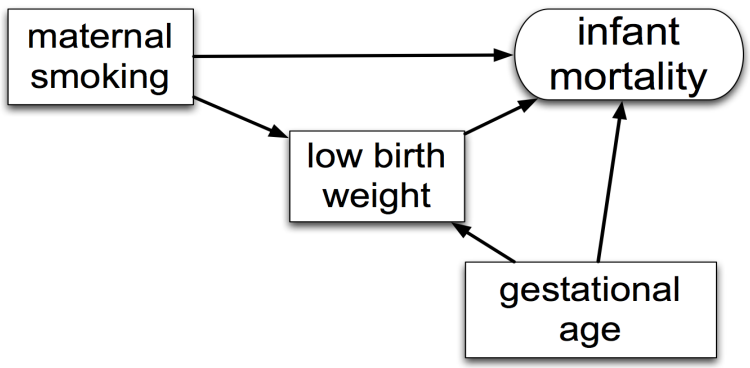
Assumptions required to estimate CDE

- No unobserved confounders C_1 of $E \rightarrow Y$
- No unobserved confounders C_2 of $M \rightarrow Y$
  - C_1 and C_2 may overlap or be distinct
  - if C_2 is affected by E, (i.e., is a causal intermediate), special methods needed



Why we need to control $M \rightarrow Y$ confounding

- Effect of smoking on infant mortality mediated by low birthweight (LBW)
- $M \rightarrow Y$ confounded by gestational age (GA)



- Maternal smoking looks protective among LBW babies if confounding of $M \rightarrow Y$ by GA left uncontrolled

Collider stratification bias

- LBW a collider on $E \rightarrow M \leftarrow C \rightarrow Y$ path
- Maternal smoking, GA inversely correlated among LBW babies, even if uncorrelated marginally
  - LBW caused by some pathologic mechanism
  - if not maternal smoking, the more likely low GA
- Induced correlation opens backdoor path from maternal smoking to infant mortality, unless we block it by controlling for GA

Estimating controlled direct effects

- When a confounder of the $M \rightarrow Y$ is also a causal intermediate, use inverse weighting (more on this soon)
- Otherwise, use regression plus standardization:
  - fit linear, logistic, Poisson, negative binomial (but not Cox) model for effect of E, M, C_1 and C_2 on Y
  - model may include $E - M$ interactions
  - in Stata, use `margins, dydx(E) at(M=m)` to estimate CDE setting $M = m$

CDE for alendronate, BMD, and vertebral fracture

Estimate effect of alendronate on vertebral fracture when change in BMD set at average level in non-users

$Y \quad E \quad M \qquad\qquad C$

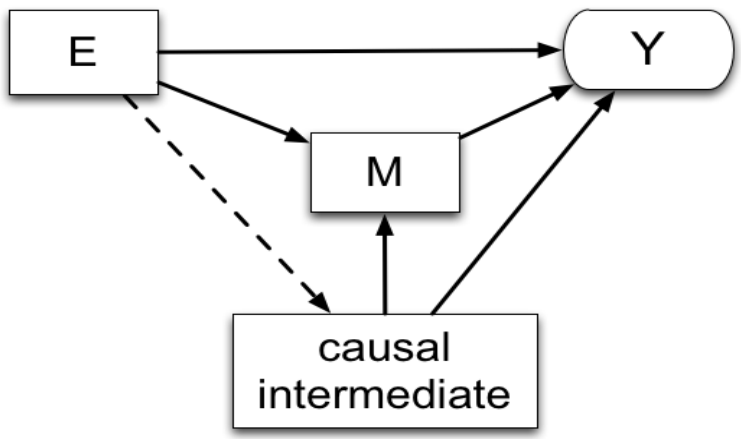
```
. qui logistic newvfx i.tx bmd_ch blbmd i.blnspfx i.blvfx i.smoking bmi_spl* age_spl*
. qui sum bmd_ch if tx==0 // average value of BMD change in placebo group
. local mean_chbmd = r(mean) // use mean as local variable in next command
. margins, dydx(tx) at(bmd_ch = `mean_chbmd')

Average marginal effects                        Number of obs   =       5324
at           : bmd_ch          =   -.0047857

------------------------------------------------------------------------------
             |            Delta-method
             |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          tx |
Alendronate  |   -.026152    .006789    -3.85   0.000    -.0394582   -.0128459
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.
```

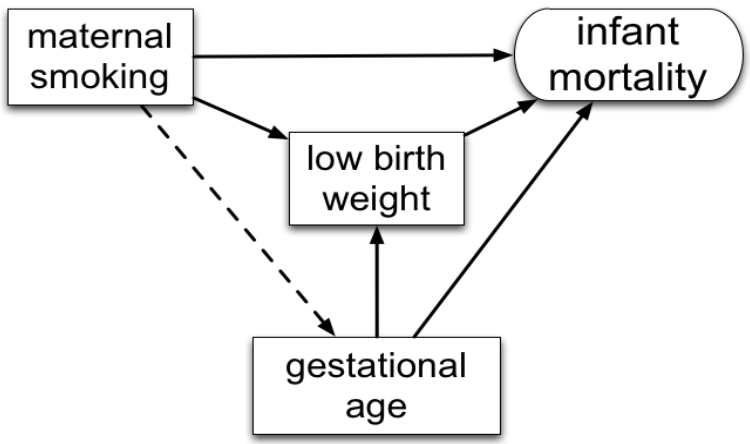
Causal intermediates

- Three ways to characterize causal intermediate:
  1. Confounder of $M \rightarrow Y$ affected by E
  2. Mediator of $E \rightarrow M$ with direct effects on Y
  3. Mediator of $E \rightarrow Y$ on another indirect path, with effects on M



Causal intermediate: example

- Gestational age (GA) confounds effect of LBW on infant mortality, and is affected by maternal smoking



- Controlling for GA removes part of direct effect of maternal smoking (i.e., effect not mediated by LBW)
- Not controlling for GA induces collider stratification bias
- Solution: inverse weighting methods

Estimation of CDE with causal intermediate

- Fit model for effects of E and M on Y, using combined stabilized weight

$$\frac{P(M = m|E = e)}{P(M = m|E = e,\ C_1 = c_1, C_2 = c_2)} \times \frac{P(E = e)}{P(E = e|C_1 = c_1)}$$

- Use `margins, dydx(E) at(M=m)` to get CDE
- Both components of weight should be checked for violations of positivity (i.e., big weights)
- Works for binary/categorical but (usually) not for continuous exposures and mediators (weights are unstable)

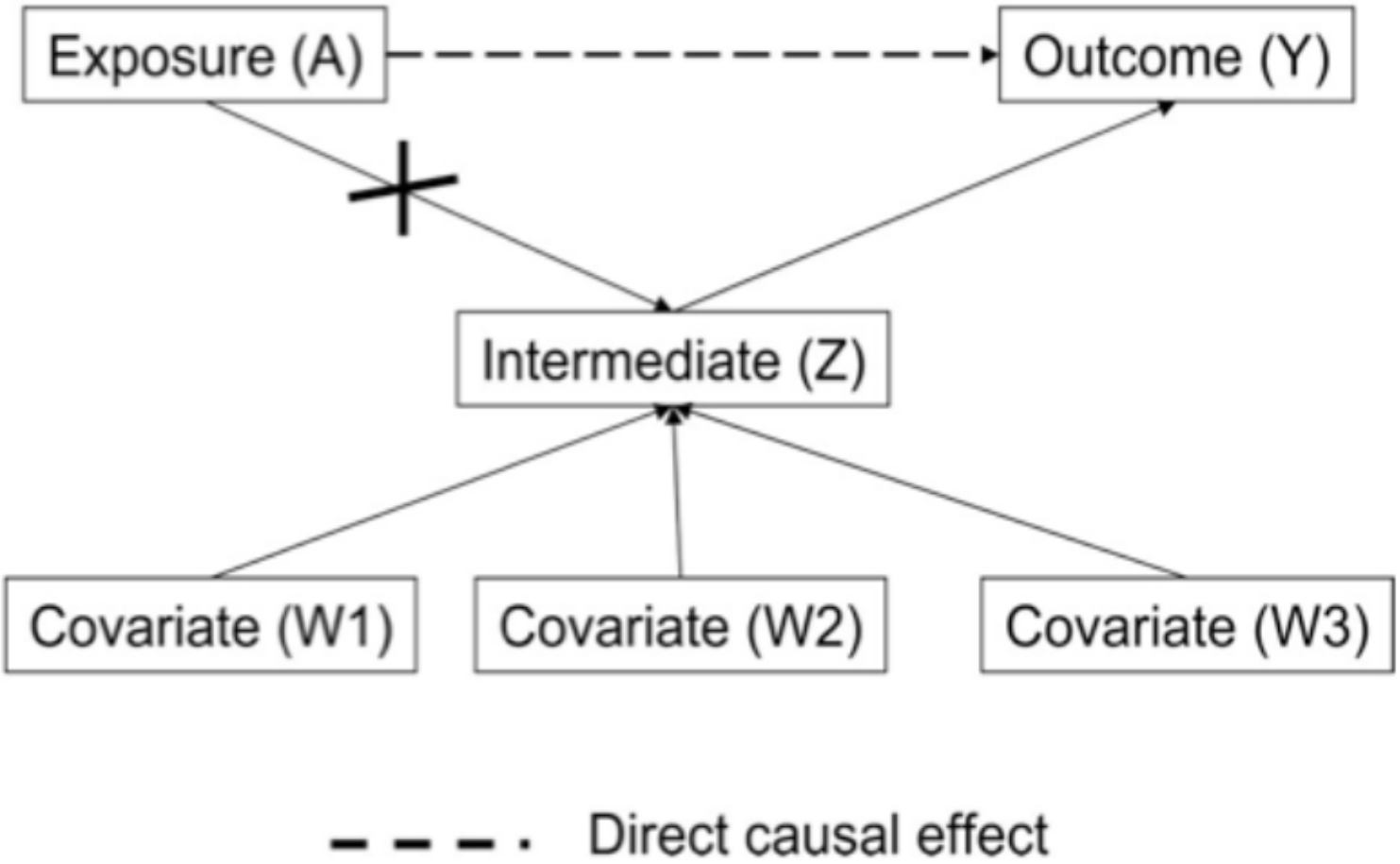
CDE: summing up

- Advantages
  - often have a clear policy interpretation
  - understandable assumptions for identifiability
- Disadvantages
  - depends on choice of level to set M, *unless there is no* $E - M$ *interaction on scale for CDE*
  - no corresponding controlled indirect effect or effect decomposition
  - intervention may not exist to cleanly set M

Natural direct effect (NDE)

- Causal effect of E with $E \rightarrow M$ pathway blocked
- Requires defining potential values of mediator $M(e)$
- Two NDEs, depending on level of E determining $M(e)$:
  - *Total NDE*: $\mathrm{E}[Y(1, M(1)) - Y(0, M(1))]$
  - *Pure NDE*: $\mathrm{E}[Y(1, M(0)) - Y(0, M(0))]$
- Causal effect of changing from $E = 0$ to $E = 1$, with M taking on natural level under exposure (total NDE) or no exposure (pure NDE)
- $E \rightarrow M$ is blocked, but other influences on M still operate

NDE: only $E \rightarrow M$ blocked



Petersen *et al.*, *Epidemiology*, 2006;17:276-84

Natural indirect effect (NIE)

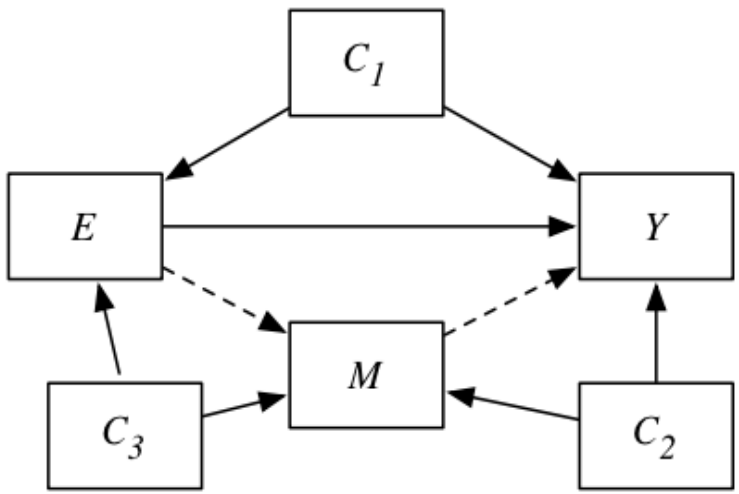
- Causal effect of E operating through M
- Two NIEs, depending on level of E
  - *Total NIE*: $\mathrm{E}[Y(1, M(1)) - Y(1, M(0))]$
  - *Pure NIE*: $\mathrm{E}[Y(0, M(1)) - Y(0, M(0))]$
- Causal effect of changing from $M(0)$ to $M(1)$, when everyone is exposed (total NIE) or no one is (pure NIE)

Effect decomposition works for NDE and NIE

- TE = pure NDE + total NIE = total NDE + pure NIE
- Algebra to show this is easy enough (give it a try!)

Assumptions required to estimate NDE and NIE

- Two assumptions also required for CDE:
  - No unobserved confounders C_1 of $E \rightarrow Y$
  - No unobserved confounders C_2 of $M \rightarrow Y$
- Two more assumptions required for NDE/NIE
  - No unobserved confounders C_3 of $E \rightarrow M$
  - No causal intermediates confound $M \rightarrow Y$



Estimating NDEs and NIEs

- Implemented using downloadable `medeff` command in Stata, based on Robins' G-formula
- NDEs are weighted averages of conditional CDEs, with weights determined by joint distribution of M and C

$$\text{pure NDE} : \sum_c \sum_m \mathrm{E}[Y(1,m) - Y(0,m)|c] P(M(0) = m|c) P[C = c]$$

$$\text{total NDE} : \sum_c \sum_m \mathrm{E}[Y(1,m) - Y(0,m)|c] P(M(1) = m|c) P[C = c]$$

- $\mathrm{E}[Y(1,m) - Y(0,m)|c]$: conditional CDE, given $C = c$, setting $M = m$
- $P(M(e) = m|c]$: conditional model used to impute $M(e)$

Example: NDEs and NIEs for vertebral fracture

```
. medeff (regress bmd_ch tx age_spl* bmi_spl* smoking blbmd blvfx blnspfx) ///
>         (logit newvfx tx bmd_ch age_spl* bmi_spl* smoking blbmd blvfx blnspfx), ///
>         mediate(bmd_ch) treat(tx)
------------------------------------------------------------------------------
        Effect                  |  Mean           [95% Conf. Interval]
--------------------------------+---------------------------------------------
        ACME1                   | -.0105528     -.0155193      -.005906
        ACME0                   | -.0156206     -.0210913     -.0099139
        Direct Effect 1         | -.0217798     -.0339505      -.010115
        Direct Effect 0         | -.0268476      -.040301     -.0126326
        Total Effect            | -.0374004     -.0494322     -.0253331
        % of Total via ACME1    |  .2826272       .213481      .4165622
        % of Total via ACME0    |   .418352      .3160001      .6166061

        Average Mediation       | -.0130867     -.0182684     -.0080889
        Average Direct Effect   | -.0243137     -.0373419     -.0113418
        % of Tot Eff mediated   |  .3504896      .2647406      .5165841
------------------------------------------------------------------------------
```

ACME1 = total NIE **ACME0** = pure NIE

Direct Effect 1 = total NDE **Direct Effect 0** = pure NDE

Total Effect = total NIE + pure NDE = pure NIE + total NDE

Average Mediation = average of total NIE and pure NIE

Average Direct Effect = average of total NDE and pure NDE

% of Tot Effect Mediated = **Average Mediation/Total Effect**

Exposure-mediator interaction

- For continuous outcomes, linear model makes it easy test for exposure-mediator interaction on absolute difference scale, our usual focus in assessing direct and indirect effects
- For binary outcomes, interaction depends on scale: no interaction on OR scale implies interaction on RD scale
  - note that we could have interaction on both scales!
- `medeff` handles exposure-mediator interactions on both scales correctly

medeff accommodates interaction on OR scale

```
. gen ix = tx*bmd_ch
. medeff (regress bmd_ch tx age_spl* bmi_spl* smoking blbmd blvfx blnspfx)  ///
> (logit newvfx tx ix bmd_ch age_spl* bmi_spl* smoking blbmd blvfx blnspfx),  ///
> mediate(bmd_ch) treat(tx) interact(ix)
```

Effect	Mean	[95% Conf.	Interval]
ACME1	-.0094215	-.0171442	-.0025262
ACME0	-.0160536	-.022994	-.0088877
Direct Effect 1	-.0213269	-.0339743	-.009626
Direct Effect 0	-.0279591	-.0419414	-.0126819
Total Effect	-.0373806	-.049113	-.0254245
% of Total via ACME1	.2506157	.1918325	.3705668
% of Total via ACME0	.4270355	.3268721	.6314255
Average Mediation	-.0127376	-.0181072	-.0075906
Average Direct Effect	-.024643	-.0372264	-.0117513
% of Tot Eff mediated	.3388256	.2593523	.5009961

Interactions and recanting witnesses

- If E and M do not interact on scale of interest
  - level at which M is set does not influence direct effect
    - CDE does not vary when M set to different values of m
    - NDE is the same with $M(0)$ or $M(1)$
  - accordingly,
    - pure NDE = total NDE = CDE
    - pure NIE = total NIE
- If there is a causal intermediate
  - CDE can be estimated using inverse weighting
  - NDE and NIE cannot be validly estimated
    - causal intermediate is a *recanting witness*

NDEs and NIEs: summing up

- Advantages
  - indirect effect well defined
  - total effect decomposes into direct and indirect effects
  - may have mechanistic interpretation
- Disadvantages
  - unlikely to be identifiable in a single RCT
  - depends on counterfactual values $M(e)$
  - causal intermediates induce bias, hard to rule out
  - Stata implementation of `medeff` limited to continuous and binary M and Y; `R` version handles survival times

Estimation methods for CDE and NDE

- CDE
  - if there is a causal intermediate, use inverse weighting
  - otherwise, fit model for effects of E, M, and C on Y, accommodating $E - M$ interaction as needed, then estimate CDE using `margins, dydx(E) at(M=m)`
- NDEs and NIEs
  - if there is no causal intermediate, estimate NDE and NIE using `medeff`
  - if there is a causal intermediate but no $E - M$ interaction (so NDE $=$ CDE), estimate CDE using inverse weighting
  - if both, NDE and NIE cannot be estimated without bias

What if we can't set E and M?

- Strict view: counterfactual approaches only make sense when E and M can be set via intervention
  - total effect only interpretable if E can be set
  - CDE only interpretable if E and M can be set
  - NDE and NIE uninterpretable because M must be set to possibly unobserved potential value $M(e)$
- Another view:
  - causal questions still make sense for unsettable exposures, mediators
  - NDE, NIE can be motivated by imagining an intervention that blocks $E \rightarrow M$, rather than setting M

Longitudinal mediation, cross-sectional data

- Recent work[1] shows that if
  - repeated values of E, M, and Y arise from random effects or auto-regressive models, and
  - $E \rightarrow M$ and $M \rightarrow Y$ effects are lagged

  then standard mediation analysis using cross-sectional data can produce badly biased estimates
- Longitudinal data must be used to get valid estimates
  - some simulations suggest that three time points, allowing lags in $E \rightarrow M$ and $M \rightarrow Y$ effects, may be enough *(preliminary results!)*

[1] Maxwell *et al.*, *Psychological Methods*, 2007:12:23-44; *Multivariate Behavioral Research*, 2011:46:816-11

Sample size calculations

- Based on joint testing of both steps in indirect pathway ($E \rightarrow M$ and $M \rightarrow Y$)[2]
- R functions accommodate
  - continuous and binary E and M
  - continuous, binary, count, and failure time Y
- Also does power, minimum detectable effects (MDEs)
- Not too hard to use, but does require multiple inputs
- Caveat: validated for cross-sectional data; *might* work for three time points with lagged E and M
- E-mail me for latest version of program including MDEs[3]

[2] Vittinghoff & Neilands, *Prevention Science*, 2014

[3] eric.vittinghoff@ucsf.edu

Summary

- Mediation requires more restrictive and difficult-to-verify assumptions than average causal effect (ACE)
- Care must be taken to
  - measure and adjust for $M \rightarrow Y$ confounders
  - rule out or identify and measure causal intermediates
- Newer methods needed if
  - exposure and mediator interact
  - outcome and/or mediator are not continuous
  - there are causal intermediates
  - mediation plays out over time