Causal Mediation Analysis

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Plan of Presentation

(1) Introduction and Motivating Example

(2) Standard mediation analysis and limitations

(3) Definitions for causal mediation analysis

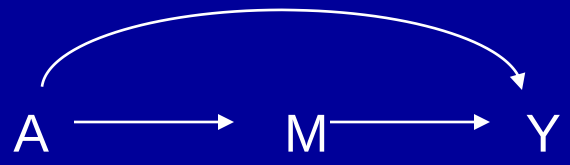
(4) Regression in causal mediation analysis

(5) Sensitivity analysis for direct and indirect effects

(6) Prenatal care example revisited

Questions of Mediation

In a number of research contexts we might be interested in the extent to which the effect of some exposure A on some outcome Y is mediated by an intermediate variable M and to what extent it is direct



Stated another way, we are interested in the direct and indirect effects of the exposure

Example

In the last 30 years…

- funding for prenatal care has increased
- utilization of prenatal care has increased
- low birth weight rates have increased!!!
- preterm birth rates have increased!!!
- infant mortality has decreased
- c-section rates have increased

Hypothesis: Prenatal care allows for the detection of early pregnancy problems for which the appropriate response may be preterm c-section or labor induction

Question: What proportion of the effect of prenatal care on infant mortality is mediated by “medically-induced preterm birth”?

Standard Approach

Example: Caffo et al. (2008) consider the extent to which the effect of cumulative lead dose, A, on cognitive function, Y , is mediated by brain volumes, M.

The standard approach to mediation analysis in much biomedical research consists of regressing the outcome Y on the exposure A and confounding factors C and then considering whether the coefficient for A changes when controlling for mediator M

Controlling for age, education, smoking, and alcohol consumption, the authors obtained an estimate for the overall effect of lead dose on 5.00 point decline (95% CI: -8.57, -1.42) in executive functioning cognitive test scores per 1μg/g increase in peak tibia lead exposure

When control is also made for the mediator, brain volumes, the estimate of the "direct effect" of lead exposure becomes a decline of 3.79 points (95% CI: -7.40, -0.18)

Because the effect decreases (from 5.00 to 3.79) when controlling for the mediator, it seems that some of the effect of lead exposure on cognitive functioning is mediated by brain volume

This gives an estimate of the indirect effect of 5.00-3.79 = 1.21 (P = 0.01)

Standard Approach

Again, the standard approach to mediation analysis in much epidemiologic and social science research consists first of regressing the outcome Y on the exposure A and confounding factors C

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

And compare the estimate ϕ_1 of exposure A with the estimate θ_1 obtained when including the potential mediator M in the regression model

$E[Y|A=a,M=m,C=c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_4' c$

If the coefficients ϕ_1 and θ_1 differ then some of the effect is thought to be mediated and the following estimates are often used:

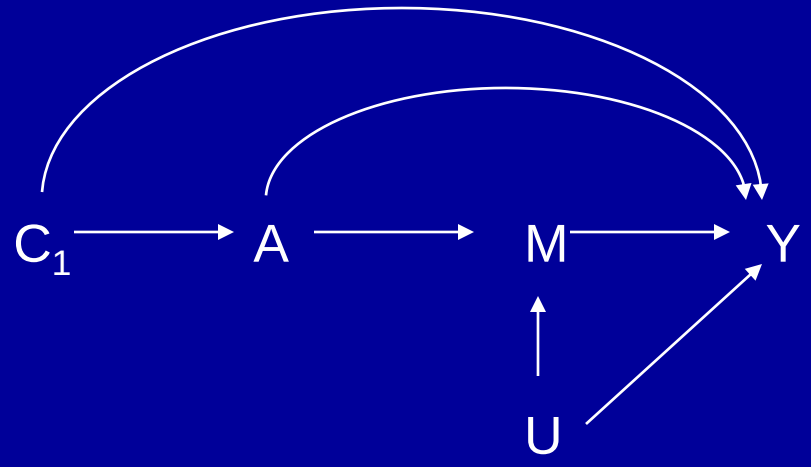
Indirect effect = $\phi_1 - \theta_1$

Direct effect = θ_1

Standard Approach

The standard approach to mediation analysis of just including the mediator in the regression is subject to two important limitations

PROBLEM 1: Even if the exposure is randomized or if all of the exposure-outcome confounders are included in the model there may be confounders of the mediator-outcome relationship



If control is not made for the mediator-outcome confounders then results from the standard approach can be highly biased

Standard Approach

PROBLEM 2: The standard approach presupposes that there are no interactions between the effects of the exposure A and the mediator M on the outcome Y i.e. it assumes the model without interactions is correctly specified:

$E[Y|A=a,M=m,C=c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_4' c$

If the true model includes an interaction:

$E[Y|A=a,M=m,C=c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4' c$

but the standard approach is used without an interaction one might conclude that all or almost all of the effect is mediated in cases in which no mediation is in fact present!

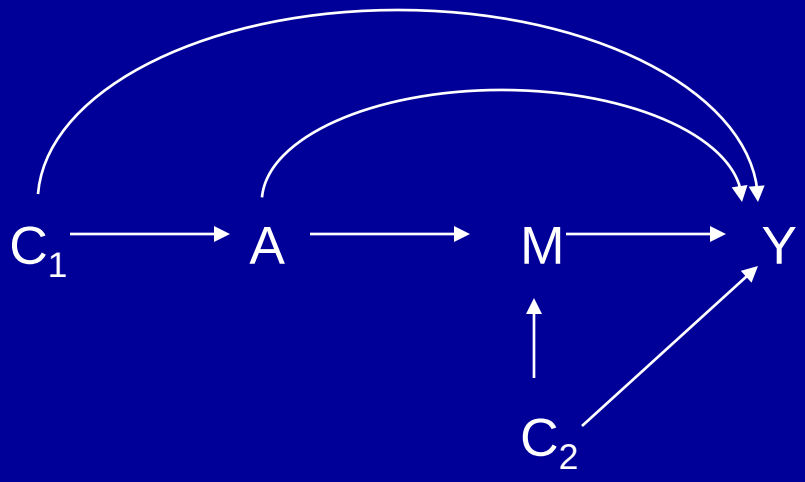
We will consider each problem is more detail…

Mediator-Outcome Confounding

In many biomedical and epidemiologic studies, careful thought is given to control for confounding of the exposure-outcome relationship; data are collected on all variables thought to confound the relationship between the exposure and the outcome (C_1 in the diagram)

However, often little thought is given to collecting data on variables that might confound the mediator-outcome relationship (C_2 in the diagram)

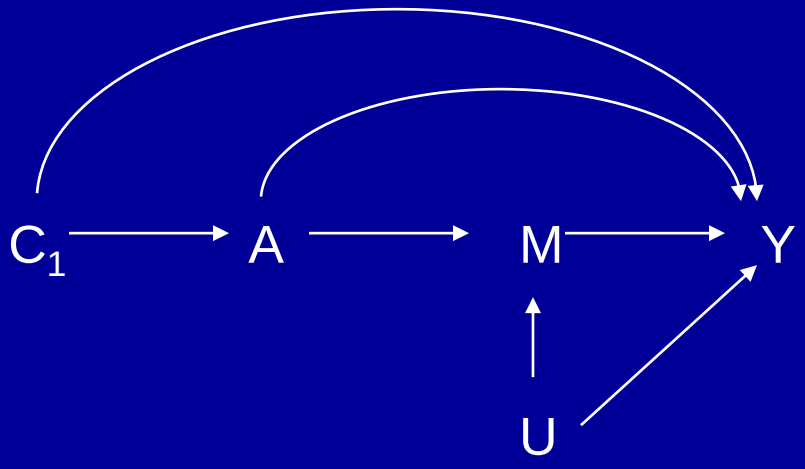
Mediation analyses are often secondary analyses in biomedical research and these variables often aren't controlled for



Mediator-Outcome Confounding

Just as unmeasured exposure-outcome confounders can generate confounding bias of estimates of overall effects

So also unmeasured mediator-outcome confounders can generate bias of estimates of direct and indirect effects

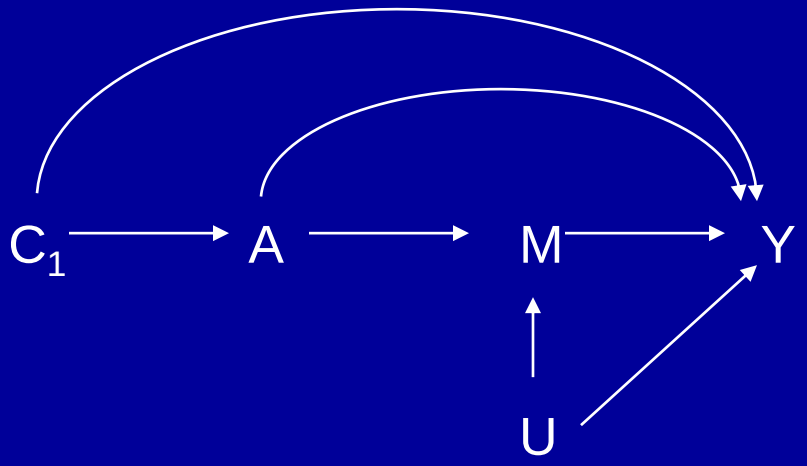


Mediator-Outcome Confounding

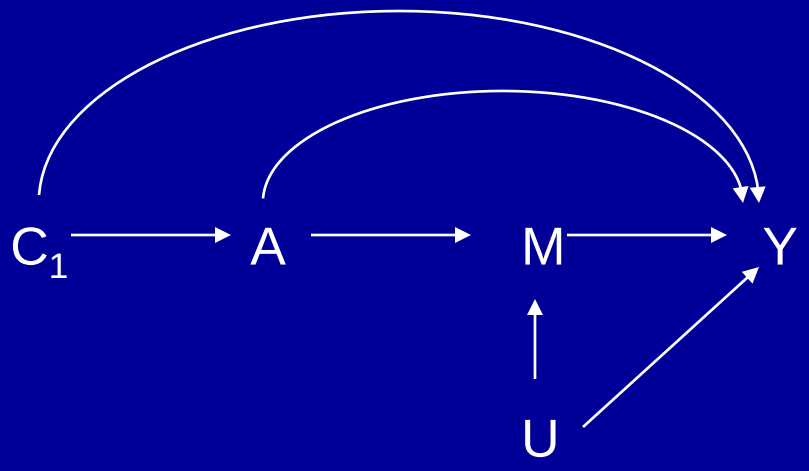
A number of studies (e.g. Wilcox, 2001; Hernandez-Diaz et al., 2006) have examined the effect of smoking A on infant mortality Y within strata of birthweight M

Conceived of in another way, this is the direct effect of smoking on infant mortality controlling for the intermediate birthweight

Studies have found that amongst those with the lowest birth weight, smoking appears to have a beneficial effect!!! e.g. the odds of infant mortality amongst infants <2000g is 0.79 lower for smoking mothers than non-smoking mothers!



Mediator-Outcome Confounding



A=maternal smoking
M=birth weight
Y=infant mortality
U=birth defect

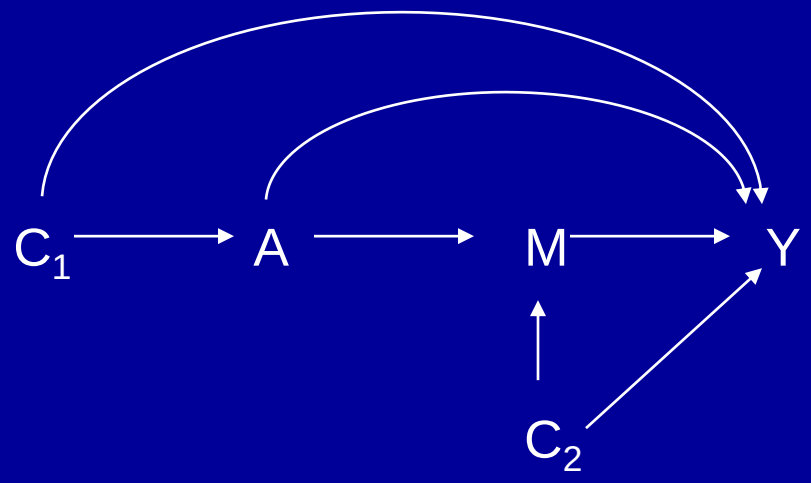
These studies have not controlled for birth defects U which confounds the mediator-outcome relationship (Hernandez-Diaz et al, 2006)

Essentially low birth weight might be due to smoking or due to birth defects; if we look at infants who have very low birth weight whose mothers do not smoke then the low birth weight is likely due to some other cause (e.g. a birth defect) that is much worse than smoking

If we were able to control for birth defects also (e.g. compare smoking and non-smoking mothers within strata of the presence of birth defect we likely would not observe these paradoxical findings)

Mediator-Outcome Confounding

If we can control for both (i) all exposure-outcome confounders C_1 and (ii) all mediator-outcome confounders C_2 then our first problem is taken care of



The importance of controlling for mediator-outcome confounders when examining direct and indirect effects has been emphasized in the causal inference literature (Robins and Greenland, 1992; Pearl, 2001; Cole and Hernan, 2002)

Mediator-Outcome Confounding

The importance of controlling for mediator-outcome confounders when examining direct and indirect effects was also pointed out early on in the psychology literature on mediation (Judd and Kenny, 1981)

However a later paper in the psychology literature (Baron and Kenny, 1986) came to be the canonical reference for mediation analysis in the social sciences (>17,000 citations on Google Scholar)

Unfortunately, the Baron and Kenny (1986) paper did not note that control needed to be made for mediator-outcome confounders in the estimation of direct and indirect effects, even though the point had been made by Judd and Kenny five years earlier in 1981 and even though the two papers shared an author

As a result the point has been ignored by most of the research on mediation in the social sciences; many of these analyses are thus likely biased (possibly severely)

Mediator-Outcome Confounding

There are essentially two approaches to address mediator-outcome confounding (ideally both will be used):

(1)If mediation analysis is going to be part of an epidemiologic study then careful thought should be given to collecting data on mediator-outcome confounding variables during the study design stage

(2)After the study is finished, if there are unmeasured mediator-outcome confounders then sensitivity analysis techniques can be used to assess the extent to which the unmeasured confounding variable would have to affect the mediator and the outcome (and possibly the exposure) in order to invalidate inferences about direct and indirect effects (VanderWeele, 2010)

Exposure-Mediator Interactions

The second potential problem with the standard approach to mediation analysis is that it generally presupposes no interactions between the effects of the exposure and the mediator on the outcome:

$E[Y|A=a,M=m,C=c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_4' c$

This can lead to invalid conclusions; to see why, suppose M were binary and the true model were:

$E[Y|A=a,M=m,C=c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4' c$

with θ_1=0.5 and θ_3= -1.0 so that the sign of the effect of the exposure was different when the mediator were present (-0.5) versus absent (+0.5)

If we fit the model without the interaction

$E[Y|A=a,M=m,C=c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_4' c$

we might estimate a value of θ_1 close to 0 because of averaging

Exposure-Mediator Interactions

Under the standard approach if we fit the model without the interaction

$E[Y|A=a,M=m,C=c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_4' c$

and estimated a value of θ_1 close to 0 then the standard conclusion would be that almost all of the effect of the exposure on the outcome was mediated because once we include the mediator in the regression the coefficient for exposure A is close to 0

But this would be completely an artifact of the interaction term $\theta_3 am$ that was ignored

Furthermore, we might have an interaction between the effects of A and M on Y even if A had no effect on Y (and thus there was no mediation)

We might thus conclude that almost all of the effect of the exposure on the outcome was mediated by M even in cases in which none of it is in fact mediated!

Exposure-Mediator Interactions

Interactions between the effects of the exposure and the mediator on the outcome create another problem for the standard approach:

Even if we include an interaction term in the regression model:

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

$E[Y|A=a,M=m,C=c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4' c$

The usual measures of direct and indirect effect

Indirect effect = $\phi_1 - \theta_1$

Direct effect = θ_1

break down because it is unclear how to handle the interaction coefficient θ_3

The definitions and models for direct and indirect effects in the social sciences presuppose no interaction between the effects of the exposure and the mediator on the outcome

Exposure-Mediator Interactions

In addition to clarifying the various no-unmeasured confounding assumptions that are need in mediation analysis, the early causal inference literature on mediation (Robins and Greenland, 1992; Pearl, 2001) provided definitions of direct and indirect effects that could be used even when there were interaction between the effects of the exposure and the mediator on the outcome and that could also be used in the presence of non-linear models

In what follows we will:

(1) Consider the causal ("counterfactual") definitions of direct and indirect effects for mediation analysis and discuss the no unmeasured confounding assumptions required for identification

(2) Describe regression methods that can be used to estimate these counterfactual direct and indirect effect quantities

(3) Provide sensitivity analysis techniques to assess the importance of possible violations to the no unmeasured confounding assumptions

Definitions

Let Y denote some outcome of interest for each individual

Let A denote some exposure or treatment of interest for each individual

Let M denote some post-treatment intermediate(s) for each individual (potentially on the pathway between A and Y)

Let C denote a set of covariates for each individual

Let Y_a be the counterfactual outcome (or potential outcome) Y for each individual when intervening to set A to a

Let Y_{am} be the counterfactual outcome Y for each individual when intervening to set A to a and M to m

Let M_a be the counterfactual outcome M for each individual when intervening to set A to a

Definitions

from Robin and Greenland (1992) and Pearl (2001)

Controlled direct effect: The controlled direct effect comparing treatment level A=a to A=a* intervening to fix M=m

$$CDE(1,0;m) = Y_{1m} - Y_{0m}$$

Natural direct effect: The natural direct effect comparing treatment level A=1 to A=0 intervening to fix $M=M_0$

$$NDE(1,0;0) = Y_{1M_0} - Y_{0M_0}$$

Natural indirect effect: The natural indirect effect comparing the effects of $M=M_1$ versus $M=M_0$ intervening to fix A=1

$$NIE(1,0;1) = Y_{1M_1} - Y_{1M_0}$$

Properties of Direct and Indirect Effects

A total effect decomposes into a direct and indirect effect:

$$Y_1 - Y_0 = Y_{1M_1} - Y_{0M_0}$$
$$= (Y_{1M_1} - Y_{1M_0}) + (Y_{1M_0} - Y_{0M_0})$$
$$= \text{NIE} + \text{NDE}$$

The <u>definitions</u> of natural direct and indirect effect do not presuppose no interactions between the effects of the exposure and the mediator on the outcome

The <u>effect decomposition</u> of a total effect into a natural direct and indirect effect also does not presuppose no interaction between the effects of the exposure and the mediator on the outcome

Properties of Direct and Indirect Effects

The “direct effects” with the standard approach are generally “controlled direct effects.” Controlled direct effects can be useful in examining the direct effects of an exposure but not in general for examining indirect effects

The difference between a total effect and a controlled direct effect does not generally give an indirect effect (Kaufman et al., 2004; VanderWeele, 2009) because there may simply be interaction between the effects of the exposure and mediator on the outcome

However, if there is no interaction between the effects of the exposure and the mediator on the outcome then the difference between a total effect and a controlled direct effect give an indirect effect (in this case of no interaction the controlled direct effect and natural direct effect coincide)

Identification of Direct and Indirect Effects

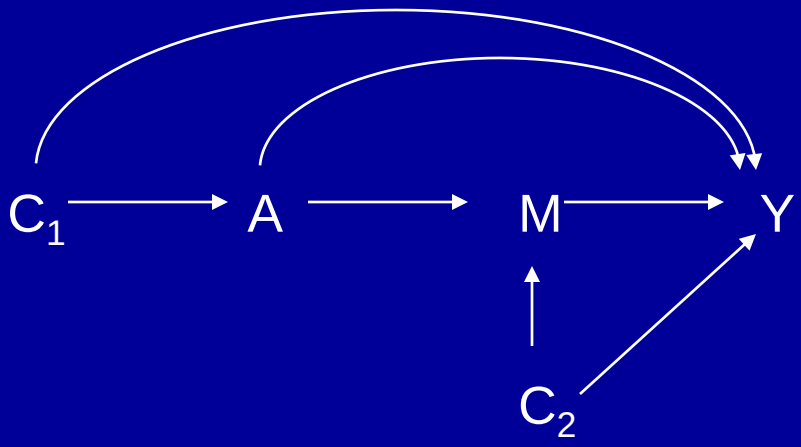
Let C be the measured covariates; to get valid estimates of controlled direct effects we need two assumptions

(1) There are no unmeasured exposure-outcome confounders given C

(2) There are no unmeasured mediator-outcome confounders given C

Formally, (1) is $Y_{am} \perp\!\!\!\perp A \mid C$ and (2) is $Y_{am} \perp\!\!\!\perp M \mid C,A$

Thus if we do not control for C_2 in the set of measured covariates C we will in general get biased estimates of the controlled direct effect



Identification of Direct and Indirect Effects

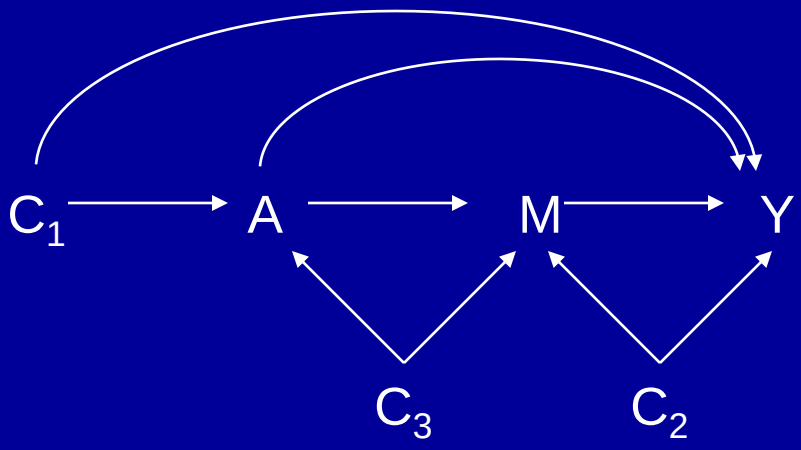
To estimate natural direct and indirect effects we need the assumptions (1) and (2) above but we also need two additional assumptions:

(3) There are no unmeasured exposure-mediator confounders given C

(4) There is no effect of exposure that confounds the mediator-outcome relationship

Formally, (3) is $M_a \perp\!\!\!\perp A \mid C$ and (4) is $Y_{am} \perp\!\!\!\perp M_{a^*} \mid C$

We need to control for the A-M confounders such as C_3 if we are interested in natural direct and indirect effects



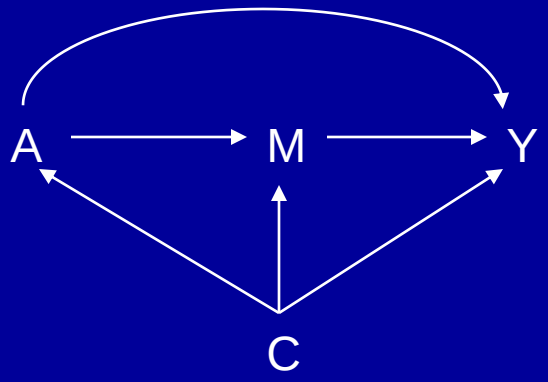
Regression for Causal Mediation Analysis

Under assumptions (1)-(4) above we can estimate controlled direct effects and natural direct and indirect effects

To do so we use two separate regressions one for the outcome Y on the exposure A, mediator M and confounding variables C…

And a second regression of the mediator M on the exposure A and the confounding variables C

The two regressions can be combined to estimate natural direct and indirect effects



Regression for Causal Mediation Analysis

The regression accommodate exposure-mediator interaction:

$E[Y|A=a,M=m,C=c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4' c$

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

We can combine the estimates from the two regression models to get the following formulas for direct and indirect effects, comparing exposure levels a and a* (VanderWeele and Vansteelandt, 2009):

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

$NDE(a,a^*;a^*) = (\theta_1+\theta_3\beta_0+\theta_3\beta_1 a^*+\theta_3\beta_2' c)(a-a^*)$

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

Similar results are available if the outcome is binary (VanderWeele and Vansteelandt, 2010)

Regression for Causal Mediation Analysis

Note that if there is no interaction between the effects of the exposure and the mediator on the outcome so that $\theta_3=0$ then these expression reduce to:

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

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

which are the expression often used for direct and indirect effects in the social science literature (Baron and Kenny, 1986)

However, unlike the Baron and Kenny (1986) approach, this approach to direct and indirect effects using counterfactual definitions and estimates can be employed even in settings in which an interaction is present

The estimates can be obtained in a relatively straightforward way using standard regression software output

Regression for Causal Mediation Analysis

Using the regression models:

$E[Y|A=a,M=m,C=c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4' c$

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

It is also possible to obtain standard errors for these expressions; for example:

$Var(CDE) = \sigma^{\theta}_{11} + 2\sigma^{\theta}_{13} m + \sigma^{\theta}_{33} m^2$

$Var(NIE) = (\theta_2+\theta_3 a)^2 \sigma^{\beta}_{11} + \beta_1^2 (\sigma^{\theta}_{22} + 2\sigma^{\theta}_{23} a + \sigma^{\theta}_{33} a^2)$

where σ^{θ}_{ij} is the covariance between estimates of θ_i and θ_j in the regression model for Y and σ^{β}_{ij} is the covariance between estimates of β_i and β_j in the regression model for M (these can be obtained from standard regression software)

The variance expression for the NDE is somewhat more complicated

Code for Mediation Regression

We first need to add a variable to the dataset for the exposure-mediator interaction term and then we need to run the mediator regression and outcome regression models

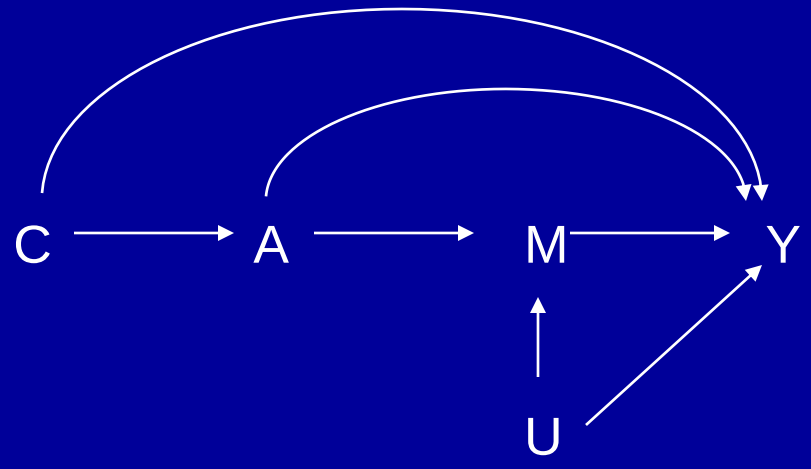
```
data mydata;
   set mydata;
   tm_int = trt*med;
run;

proc reg data=mydata;
   model med = trt c1 c2 c3 c4 c5 / covb;
run;

proc reg data=mydata;
   model y = trt med tm_int c1 c2 c3 c4 c5 / covb;
run;
```

Sensitivity Analysis

If there is an unmeasured confounding of the mediator-outcome (or exposure-outcome) relationship one can use sensitivity analysis techniques (VanderWeele, 2010) to examine the extent to which the unmeasured confounder would have to affect both the mediator and the outcome to invalidate conclusions about direct and indirect effects



Techniques are available for both controlled direct effects and natural direct and indirect effects in a broad range of settings

Here we will consider a technique for CDEs under simplifying assumptions

Sensitivity Analysis

Suppose controlling for (C,U) would suffice to control for confounding but that no data is available on U and U is a confounding variable of the mediator-outcome relationship

If we wanted to estimate controlled direct effects and adjusted only for C we would obtain

$$\sum_c \{E[Y|a,m,c] - E[Y|a^*,m,c]\}P(c)$$

The difference between this expression and the true controlled direct effect (if it were possible to adjust for C and U) is

$$Bias(CDE_{a,a^*}(m)) = \sum_c \{E[Y|a,m,c] - E[Y|a^*,m,c]\}P(c) - E[Y_{am} - Y_{a^*m}]$$

It is possible to show that for any fixed reference value u' of U we have that this bias is equal to:

$$\sum_c \sum_u \{E[Y|a,m,c,u] - E[Y|a,m,c,u']\}\{P(u|a,m,c) - P(u|a,c)\}P(c)$$
$$-\sum_c \sum_u \{E[Y|a^*,m,c,u] - E[Y|a^*,m,c,u']\}\{P(u|a^*,m,c) - P(u|a^*,c)\}P(c)$$

Sensitivity Analysis

Under some simplifying assumptions the expression becomes considerably more straightforward

For fixed level m, if γ denotes the effect of the binary unmeasured confounder U on the outcome for individuals with mediator level m and all levels of exposure (i.e. no U*A interaction so that):

$$E[Y|a,m,c,U=1]-E[Y|a,m,c,U=0]=\gamma$$

And if δ denotes the difference in the prevalence of U between the exposed subjects with mediator level m and the unexposed subjects with mediator level m, i.e. $P(u|a,m,c)-P(u|a^*,m,c)=\delta$ then the bias is given by:

$$Bias(CDE_{a,a^*}(m))=\delta\gamma.$$

i.e. one can subtract the quantity $\delta\gamma$ from the potentially confounded estimate to obtain a valid estimate of the direct effect of the exposure on the outcome with the mediator set to level m

Sensitivity Analysis

Simple sensitivity analysis bias formula: $Bias(CDE_{a,a^*}(m)) = \delta\gamma.$

If there is no interaction between the the effects of the exposure and the mediator on the outcome then this bias formula holds also for the natural direct effect and the bias for the natural indirect effect is then given simply by: - $\gamma\delta$

If there are interactions between the effects of the exposure and the mediator on the outcome or if U affect A as well and M and Y then other bias formulas hold can be used for sensitivity analysis for natural direct and indirect effects (VanderWeele, 2010)

Prenatal Care Application

(Joint work with Diane Lauderdale (U of C) and John Lantos (Kansas))

Hypothesis: Prenatal care allows for the detection of early pregnancy problems for which the appropriate response may be preterm c-section or labor induction

This might give rise to the trends of (i) rising prenatal care, (ii) rising preterm birth and low birth rate rates, (iii) rising c-section but (iv) falling infant mortality

Question: What proportion of the effect of prenatal care on infant mortality is mediated by “medically-induced preterm birth”?

Challenge: Pregnancy complications or birth defects may affect receipt of prenatal care, medically induced preterm birth and infant mortality

If data is not available or is not adequate for this potentially confounding variable, analyses addressing this question will be subject to bias

Definitions

Let Y denote infant mortality

Let A denote prenatal care

Let M denote medically induced preterm birth

Let C denote maternal age, race, education, place of birth, marital status, drinking, tobacco use, gravidity as well as plurality and geographic region of the country

Linked birth infant mortality files from the NCHS for 2003 are used in the analysis

These data have the advantage of being all US births and having a number of sociodemographic variables but have the disadvantage of inaccuracies on birth certificates records

Prenatal Care Application

We will briefly discuss the exposure and mediator variables

Several prenatal care indices (Kessner, GINDEX, APNCU) have been used in empirical analysis of birth outcomes

These indices use (i) number of prenatal care visits for gestational age, (ii) month prenatal care began

The APNCU or “Kotelchuck” (1994) index is now regularly used

Uses 2 months blocks rather than trimester (Kessner, GINDEX) to categorize care into inadequate, unknown, intermediate, adequate and adequate plus category (Kotelchuck, 1994)

“Adequate plus” care is thought to often indicate high risk pregnancies and is distinguished from “adequate”

Prenatal Care Application

The APNCU or “Kotelchuck” index has perhaps become most popular (it is now included in the NCHS birth certificate files)

Koroukian and Rimm (2002) criticized the index because an adequate plus categorization requires only 1.1 times the number expected based on ACOG recommended visits

For births with shorter gestational age, just one extra visit gives an adequate plus categorization

They argue this will bias results in birth outcomes analyses

We use a correction of the APNCU that requires at least two extra visits above ACOG recommendation for an adequate plus categorization to address this critique (VanderWeele at al., 2009) and collapses “inadequate” and “intermediate” into “not adequate” giving rise to the categories:

(1) No Adequate (2) Adequate (3) Superadequate (4) Missing

Prenatal Care Application

The potential mediator, medically induced preterm birth is considered present for c-section or inductions prior to 37 weeks gestation

A medically induced preterm birth would be standard of care for a pregnancy complication such as preeclampsia

Two Qualifications:

(1)Not all c-sections or inductions prior to 37 weeks are medically induced; spontaneous labor may occur before 37 weeks and c-section or induction may be undertaken because of prolonged labor

- we use data on induction but not augmentation
- but it generally difficult to identify cases of prior labor from the NCHS data

(2) Medically induced preterm birth may not always be medically indicated

Prenatal Care Application

A – prenatal care

M – medically induced PT birth

U – pregnancy complication

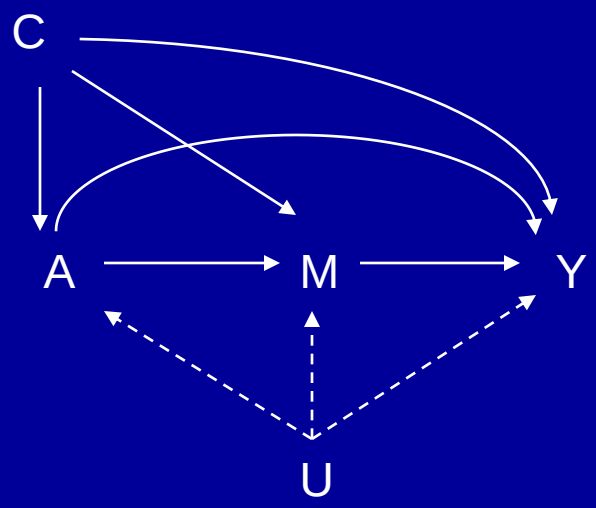
Y – infant mortality

C – sociodemographic variables

To assess mediation we need not just treatment-outcome confounders but also all mediator-outcome confounders

Pregnancy complications may increase prenatal care, the likelihood of medically indicated preterm birth and of infant mortality (NCHS files have limited data on such complications)

We will use sensitivity analysis to assess **<u>unmeasured confounding</u>**



Prenatal Care Application

Superadequate prenatal care has increased from 19.5% in 1985 to 30.0% in 2004

We use data from 2003 for which linked birth certificate infant mortality files are available

We first consider the overall effects of prenatal care on infant mortality

After control for covariates the adjusted odds ratios for infant mortality:

Adequate vs. Inadequate:	0.58 (95% CI: 0.57, 0.60)
Superadequate vs. Inadequate:	0.98 (95% CI: 0.95, 1.00)

The association with adequate is probably a combination of an effect of prenatal care and confounding by e.g. SES

The association with superadequate is probably a combination of an effect of prenatal care and an indication of a pregnancy complication

Prenatal Care Application

For the purposes of the mediation analysis we will consider the comparison of superadequate versus inadequate care; the superadequate category likely consists of those with high risk pregnancies / pregnancy complications for which medically induced preterm birth may be protective

After control for covariates the adjusted odds ratios for infant mortality comparing prenatal care and medically induced PT birth (with inadequate care / no medically induced PT birth as reference) are:

Superadequate:	0.99 (95% CI: 0.96, 1.02)
MIPB:	5.0 (95% CI: 4.8, 5.2)
MIPB*Superadequate:	0.62 (95% CI: 0.59, 0.66)

There seems to be negative **interaction** b/w superadequate care and MIPB; this may suggest the MI PT Birth is medically indicated

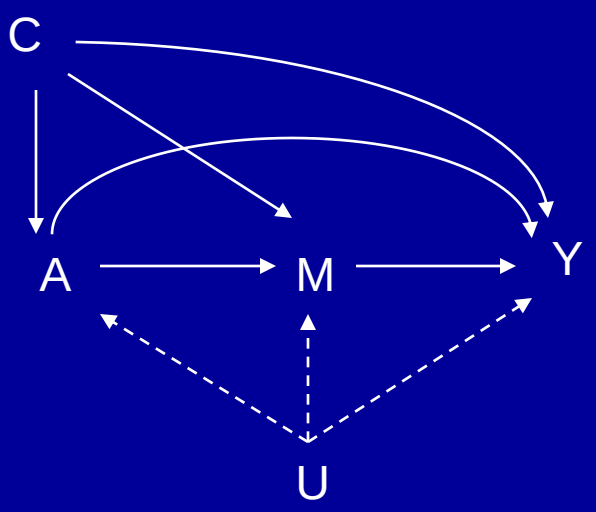
The odds of 0.99*5.0*0.66 = 3.07 is likely a combination of the protective effect of prenatal care and medically induced birth along with the increased risk of pregnancy complications

Prenatal Care Application

After control for covariates the adjusted odds ratio for medically induced preterm birth comparing superadequate and inadequate care is:

Superadequate vs. Not Adequate: 2.41 (95% CI: 2.39, 2.43)

This is likely a combination of
(i) superadequate care giving rise to the detection of pregnancy complication for which the appropriate response is medically induced preterm and
(ii) the superadequate care group consisting of more high risk pregnancies to begin with



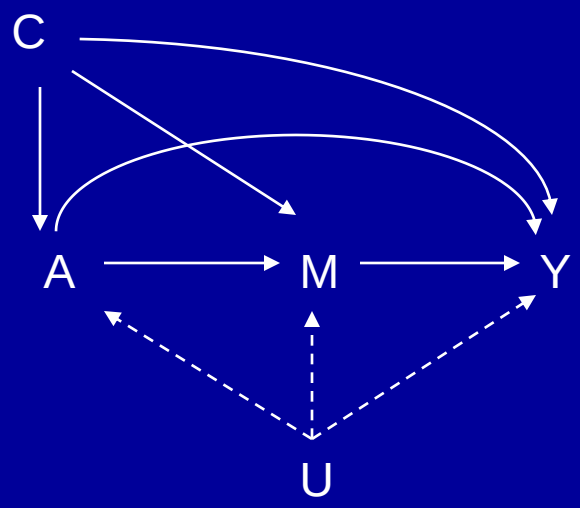
Prenatal Care Application

To assess the proportion of the effect of prenatal care on infant mortality mediated by medically-induced preterm birth we use natural indirect effect odds ratios (VanderWeele and Vanseelandt, 2010), similar to the natural indirect effects considered but on the OR scale

i.e. we compare two scenarios, both in which everyone would have superadequate prenatal care but comparing what would have happened to infant mortality if decisions about medically induced preterm birth had been made with the information available under superadequate vs. not adequate care

We control for sociodemographic variables but do not have data on prengancy complications / birth defects

Our initial estimates will be biased



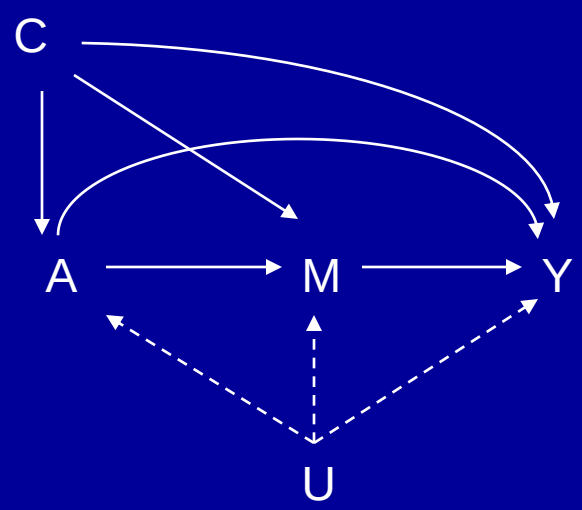
Prenatal Care Application

Adjusting for sociodemographic variable and allowing for interaction (VanderWeele and Vansteelandt, 2010) the initial biased estimate of the natural indirect effect odds ratio is:

NIE OR: 0.99 (95% CI: 0.97, 1.02)

Those with superadequate care are more likely to have MIPT birth but amongst those with MIPT birth are less at risk for infant mortality with superadequate care than with inadequate

If we use sensitivity analysis for the NIE OR and assume that U doubles the risk of infant mortality with a prevalence amongst those with superadequate care of 20% for those with MIPT birth and 5% for those without and 4 times as likely amongst those with superadequate care than those with inadequate care…



Prenatal Care Application

Under these sensitivity analysis parameters the estimates for the NIE OR and the total effect OR comparing superadequate and inadequate care are

NIE OR: 0.97 (95% CI: 0.95, 0.99)
Total Effect OR: 0.86 (95% CI: 0.83, 0.88)

About 20% of the effect (which is itself modest) would then be mediated by MIPT birth

Ongoing work will examine a range of sensitivity analysis parameters We will also consider allowing the effect of the unmeasured confounding U to vary according to whether MIPT birth was present or absent

Generally those values of the sensitivity analysis parameters that change NIE OR also change the total effect OR and a range of different sensitivity analysis parameters suggest about 20% of the effect is mediated

Conclusions

(1) For mediation analysis it is important to consider possible mediator-outcome confounding variables not just exposure-outcome confounding variables

(2) For mediation analysis it is important to consider possible exposure-mediator interactions

(3) The causal definitions of direct and indirect effect generalize the definitions in the Baron and Kenny approach and allow for interactions

(4) Study design considerations and sensitivity analysis for direct and indirect effects can help address the problem of mediator-outcome confounding variables in the analysis of direct and indirect effects

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