Plan of the Course

1. Concepts of Mediation

2. Regression Approaches

3. Sensitivity Analyses

4. Mediation and Interaction: An Application
1. Mediation - Concepts and Identification
Outline

1. Traditional approaches to mediation analysis
2. Limitations of traditional approaches
3. Counterfactual approach to mediation - definitions
4. Counterfactual approach to mediation - identifiability
Mediation Analysis, the questions of interest

Let,

\(A\) be an exposure of interest,
\(M\) be an intermediate,
\(Y\) be an outcome.
Impact

- Relevant across the Biomedical, Environmental and Social Sciences
- Etiology
- Prevention Science
- Policy Making
Motivating Example

The Etiology of Lung cancer: Fisher’s Hypothesis (1958)

Cornfield (1959) using sensitivity analyses makes strong case for causal interpretation of the association between smoking and lung cancer
Genetic variants on 15q25.1

- In 2008, three GWAS studies (Thorgeirsson et al., 2008; Hung et al., 2008; Amos et al., 2008) identified variants on chromosome 15q25.1 that were associated with increased risk of lung cancer.

- These variants had also been shown to be associated with smoking behavior (average cigarettes per day) e.g. through nicotine dependence (Saccone et al., 2007; Spitz et al., 2008).
Genetic variants on 15q25.1

- There was debate as to whether the effect on lung is direct or operates through pathways related to smoking behavior (Chanock and Hunter, 2008)

- Of the three studies that initially reported the association between the variants and lung cancer, two suggested that the association was direct (Hung et al.; Amos et al.) and one that it was perhaps primarily through nicotine dependence (Thorgeirsson et al.)

- It was also suggested that there may be gene-environment interaction (Thorgeirsson et al., 2008; Thorgeirsson and Stefanson, 2010; Le Marchand, 2008)
The study population of 1836 cases and 1452 controls is from a case control study (cf. Miller et al., 2002) assessing the molecular epidemiology of lung cancer, which began in 1992 at MGH.

Eligible cases included any person over the age of 18 years, with a diagnosis of primary lung cancer that was further confirmed by an MGH lung pathologist.

The controls (with no previous history of cancer) were recruited from among the friends or spouses of cancer patients or the friends or spouses of other surgery patients in the same hospital.
## Study Population

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<th></th>
<th>Cases (N=1836)</th>
<th>Controls (N=1452)</th>
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<tr>
<td>Average Cigarettes per Day</td>
<td>25.42</td>
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<td>Smoking Duration</td>
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<td>Age</td>
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<td>50.1%</td>
<td>56.1%</td>
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<tr>
<td>rs8034191 C alleles</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>43.3%</td>
</tr>
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<td>17.7%</td>
<td>13.0%</td>
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</table>
Association of genetic variants with lung cancer

Associations between rs8034191 C alleles and lung cancer adjusted for smoking intensity, duration, age, sex, and education gave:

\[ \text{OR} = 1.35 \ (1.21, \ 1.52) \quad P = 3 \times 10^{-7} \]

Similar to prior studies (Thorgeirsson et al., 2008; Hung et al., 2008; Amos et al., 2008)
Association of genetic variants with cigarettes per day

Associations between rs8034191 C alleles and cigarettes per day adjusting for smoking duration, age, sex and education gave:

\[
\text{Cigarettes / day} = 1.25 \ (0.00, \ 2.49) \ P=0.05
\]

Again similar to other studies
Let $Y$ denote lung cancer status, $A$ denote the genetic variant, and $M$ denote smoking status.

If we fit the logistic regression we get:

$$\logit\{P(Y = 1|A = a, M = m)\} = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4 c$$

$\theta_1 = 0.04, \ (-0.33, 0.41); \ \theta_2 = 1.33, \ (1.01, 1.64); \ \theta_3 = 0.49, \ (0.09, 0.89);$

Similar to prior studies (Li et al., 2010)
Attributing Effects to Mediating Mechanisms

The effect of $A$ on $Y$ decomposes into two parts:

1. The effect of $A$ on $Y$ through $M$
2. The effect of $A$ on $Y$ through pathways independent of $M$

Question: Is the effect on lung cancer of genetic variants on 15q25.1 mediated by nicotine dependence or is there a direct effect?

VanderWeele et al. (2012) addressed this question using definitions of direct and indirect effects that arise under the counterfactual framework (Greenland and Robins, 1992; Pearl, 2001) and methods for causal mediation analysis (VanderWeele and Vansteelandt, 2010)
Attributing Effects to Interaction

Mediating and Interactive mechanisms might operate simultaneously.

Let \( p_{am} = P(Y = 1|A = a, M = m) \)

For a binary genetic variant status and smoking status, we can decompose the joint effect of both exposures as follow:

\[
p_{11} - p_{00} = (p_{10} - p_{00}) + (p_{01} - p_{00}) + (p_{11} - p_{10} - p_{01} + p_{00})
\]
Attributing Effects to Interaction

Let $p_{am} = P(Y = 1 | A = a, M = m)$

$$p_{11} - p_{00} = (p_{10} - p_{00}) + (p_{01} - p_{00}) + (p_{11} - p_{10} - p_{01} + p_{00})$$

We can decompose the joint effect of both exposures into a component that is due to

(i) the effect that is due to just the first, and
(ii) that is due to just the second and
(iii) that is due to their interaction

At the end of the class we will reconcile mediating and interactive mechanisms.
We will investigate their role in the genetic epidemiology case study this afternoon.
Challenges in Mediation Analysis

1. Mathematical definition of causal effects

2. Identifiability

3. Complex Data
   - Non-continuous outcome and/or mediator
   - Exposure-mediator interactions
   - Measurement error
A bit of history

- Sewall Wright (1921)
- Baron and Kenny (1986)
- Greenland and Robins (1992)
- Pearl (2001)
Traditional Approach to Mediation Analysis

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 $\phi_1$ of exposure $A$ with the estimate $\theta_1$ 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 $\phi_1$ and $\theta_1$ 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 $= \theta_1$
Traditional Approach to Mediation Analysis

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, $M$.

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 1$\mu g/g$ 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).

This gives an estimate of the indirect effect of $5.00 - 3.79 = 1.21$ ($P = 0.01$).
Traditional Approach to Mediation Analysis

Using the difference between the two coefficients is sometimes called the "difference method"; it is used with some frequency in epidemiology.

Another standard method, used more commonly in the social sciences is sometimes referred to as the "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 \( A \): \[ E[Y|A = a, M = m, C = c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_4 c \]

The direct effect is once again \( \theta_1 \)

The indirect or mediated effect is the product of the coefficient of \( A \) in the regression for \( M \) times the coefficient of \( M \) in the regression for \( Y \): \( \theta_2/\beta_1 \)
Traditional Approach to Mediation Analysis

- Definition of direct and indirect effects is model driven

- Under joint normality Product Method and Difference Method estimators coincide (McKinnon, 2005)
Traditional Approach to Mediation Analysis

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.
Mediator-Outcome Confounding

A number of studies (e.g. Yerushalmy, 1971; Wilcox, 1993; Hernandez-Diaz et al., 2006) have examined the effect of smoking $A$ on infant mortality $Y$ within strata of birthweight $M$

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. in the US, the odds of infant mortality amongst infants $<$2000g is 0.79 lower for smoking mothers than non-smoking mothers!
These studies have not controlled for birth defects $U$ which confounds the mediator-outcome relationship (Hernandez-Diaz et al, 2006)

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 that is much worse than smoking

Probability of mortality for infants with low birth weight whose mother don’t smoke relative to low birth weight whose mother smoke because groups are different (first group has higher probability of birth defect)

If we were able to control for birth defects also we likely would not observe these paradoxical findings.
Mediator-Outcome Confounding

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

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.

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; Imai et al. 2010; Hafeman, 2011; Tchetgen Tchetgen and Shpitser, 2012).
PROBLEM 2: The standard approach 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 \( \theta_1 = 0.5 \) and \( \theta_3 = -1.0 \) so that the sign of the effect of the exposure was different when the mediator were absent (+0.5) versus present (-0.5)

If we fit the model without the interaction we might estimate a value of \( \theta_1 \) close to 0 because of averaging
Exposure-Mediator Interaction

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 \( \theta_1 \) close to 0 then the standard conclusion from the "difference method" 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!
Issues of Statistical Approach in presence of non linearities

- Even if we include an interaction term in the regression model the usual measures of direct and indirect effect break down because it is unclear how to handle the interaction coefficient.

- Product Method and Difference Method do not yield the same result when exposure-mediator interaction is present.

- Product Method and Difference Method estimators for direct and indirect effects are not defined when mediator is binary.

- Difference Method estimator for direct and indirect effect is not defined when the outcome is binary.

- Product Method and Difference Method do not allow for causal interpretation.
Counterfactual Framework for Causal Mediation Analysis: Motivation

- Non parametric definition of Direct and Indirect causal effects
- Effect decomposition
- Non parametric identifiability assumptions
Notation

- $Y =$ outcome of interest for each individual

- $A =$ exposure or treatment of interest for each individual

- $M =$ post-treatment intermediate(s) for each individual (potentially on the pathway between $A$ and $Y$)

- $C =$ set of covariates for each individual

- $Y_a =$ counterfactual outcome (or potential outcome) $Y$ for each individual when intervening to set $A$ to $a$

- $Y_{am} =$ counterfactual outcome $Y$ for each individual when intervening to set $A$ to $a$ and $M$ to $m$

- $M_a =$ counterfactual post-treatment intermediate(s) $M$ for each individual when intervening to set $A$ to $a$
Definitions

From Robins and Greenland (1992) and Pearl (2001)

Total effect: The total effect comparing treatment level $A = 1$ to $A = 0$

$$TE = Y_1 - Y_0$$

Controlled direct effect: The controlled direct effect comparing treatment level $A = 1$ to $A = 0$ setting $M = m$

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

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

$$NDE = Y_{1M_0} - Y_{0M_0}$$

Natural indirect effect: The natural indirect effect comparing the effects of $M = M_1$, versus $M = M_0$ setting $A = 1$

$$NIE = Y_{1M_1} - Y_{1M_0}$$
Properties of Direct and Indirect effects

A total effect decomposes into a direct and indirect effect:

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

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

The effect decomposition 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.

Natural direct and indirect effects are useful for effect decomposition; in general, controlled direct effects are not.
Properties of Direct and Indirect effects

- Controlled direct effects will often be of greater interest in evaluating policy interventions (Pearl, 2001; Robins, 2003); they can be used to assess whether there are any pathways not through the mediator.

- Natural direct and indirect effects will often be of greater interest in assessing the extent to which the effect of treatment on an outcome operates through various mechanisms (Robins, 2003; Joffe et al., 2007; Hafeman and Schwartz, 2009); they can be used for assessing mediation and for effect decomposition.
Examples

<table>
<thead>
<tr>
<th>Individual</th>
<th>$M_0$</th>
<th>$M_1$</th>
<th>$Y_{00}$</th>
<th>$Y_{10}$</th>
<th>$Y_{01}$</th>
<th>$Y_{11}$</th>
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</tbody>
</table>

For individual 1 (Total Effect completely Direct, No exposure-mediator interaction):

\[
\text{TE} = Y_1 - Y_0 = Y_{1M_1} - Y_{0M_0} = Y_{11} - Y_{00} = 1 - 0 = 1
\]
\[
\text{CDE}(m=0) = Y_{10} - Y_{00} = 1 - 0 = 1
\]
\[
\text{CDE}(m=1) = Y_{11} - Y_{01} = 1 - 0 = 1
\]
\[
\text{NDE} = Y_{1M_0} - Y_{0M_0} = Y_{10} - Y_{00} = 1 - 0 = 1
\]
\[
\text{NIE} = Y_{1M_1} - Y_{1M_0} = Y_{11} - Y_{10} = 1 - 1 = 0
\]
### Examples

<table>
<thead>
<tr>
<th>Individual</th>
<th>$M_0$</th>
<th>$M_1$</th>
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</table>

For individual 2 (No total effect, exposure-mediator interaction):

\[
\begin{align*}
\text{TE} &= Y_1 - Y_0 = Y_{1M_1} - Y_{0M_0} = Y_{11} - Y_{01} = 0 - 0 = 0 \\
\text{CDE}(m=0) &= Y_{10} - Y_{00} = 1 - 0 = 1 \\
\text{CDE}(m=1) &= Y_{11} - Y_{01} = 0 - 0 = 0 \\
\text{NDE} &= Y_{1M_0} - Y_{0M_0} = Y_{11} - Y_{01} = 0 - 0 = 0 \\
\text{NIE} &= Y_{1M_1} - Y_{1M_0} = Y_{11} - Y_{11} = 0 - 0 = 0
\end{align*}
\]
### Examples

<table>
<thead>
<tr>
<th>Individual</th>
<th>$M_0$</th>
<th>$M_1$</th>
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For individual 3 (Total effect completely mediated, exposure-mediator interaction):

\[
\begin{align*}
\text{TE} &= Y_1 - Y_0 = Y_{1M_1} - Y_{0M_0} = Y_{11} - Y_{00} = 1 - 0 = 1 \\
\text{CDE}(m=0) &= Y_{10} - Y_{00} = 0 - 0 = 0 \\
\text{CDE}(m=1) &= Y_{11} - Y_{01} = 1 - 0 = 1 \\
\text{NDE} &= Y_{1M_0} - Y_{0M_0} = Y_{10} - Y_{00} = 0 - 0 = 0 \\
\text{NIE} &= Y_{1M_1} - Y_{1M_0} = Y_{11} - Y_{10} = 1 - 0 = 1
\end{align*}
\]
Missing data issue in mediation analysis

These counterfactual definitions of direct and indirect effects are theoretically appealing.

But they are counterfactual definitions and we are not in general able to observe all the counterfactuals needed to calculate these effects.

Consider binary $A$ and $M$:

<table>
<thead>
<tr>
<th>Individual</th>
<th>$A$</th>
<th>$M_0$</th>
<th>$M_1$</th>
<th>$Y_{00}$</th>
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</table>
Mediation Analysis under Counterfactual Framework

We are able to estimate causal effects on average

\[ CDE(m) = E[Y_{1m} - Y_{0m} | C] \]
\[ NDE = E[Y_{1M_0} - Y_{0M_0} | C] \]
\[ NIE = E[Y_{1M_1} - Y_{1M_0} | C] \]
\[ TE = NDE + NIE \]

(Robins and Greenland, 1992; Pearl, 2001)
Motivation for Studying Mediation

(1) Scientific understanding and explanation
   E.g. Do genetic variants affect lung cancer through smoking or independently?

(2) Confirmation or refutation of theory
   E.g. Does low early SES affect adult health principally by setting an economic trajectory later in life?

(3) Limiting the effects of exposure by intervening on a mediator
   - E.g. Can we eliminate the effects of antipsychotic medication on mortality by preventing the primary mechanism for mortality?
Motivation for Studying Mediation

Refinement of Interventions

(4a) Improving components of an intervention to target mechanism
E.g. Will refining an educational to better target classroom quality improve educational outcomes?

(4b) Eliminating costly ineffective components of an intervention
E.g. Does a CBT intervention improve depressive symptoms only through antidepressant use?

(4c) Understanding why an intervention failed
E.g. Did the intervention not affect the mediator, or does the mediator not affect the outcome, or was the direct effect in the opposite direction of the mediated effect??
IDENTIFIABILITY ASSUMPTIONS:

(i) No unmeasured exposure-outcome confounding given C
(ii) No unmeasured mediator-outcome confounding given C
(iii) No unmeasured exposure-mediator confounding given C
(iv) No effect of exposure that confounds the mediator-outcome relationship

Note that assumptions (i) and (iii) are satisfied automatically if the exposure is randomized but not (ii) and (iv).
Under assumptions (1) and (2) the controlled direct effect conditional on the covariates is given by:

\[ E[CDE(m) | C = c] = E[Y | A = 1, M = m, C = c] - E[Y | A = 0, M = m, C = c] \]

Under assumptions (1)-(4) the conditional natural direct effect is:

\[ E[NDE | C = c] = \sum_m \{ E[Y | A = 1, m, c] - E[Y | A = 0, m, c] \} P(M = m | A = 0, c) \]

Under assumptions (1)-(4) the conditional natural indirect effect is:

\[ E[NIE | C = c] = \sum_m E[Y | A = 1, m, c] \{ P(M = m | A = 1, c) - P(M = m | A = 0, c) \} \]

These are the effects within strata of the covariates. We could take averages over each stratum weighted by the probability \( P(C = c) \) to get population averages of the effects.
Summary

- Standard approaches to mediation analysis (e.g. the difference method in epidemiology) are subject to the problems of (i) unmeasured mediator-outcome confounding and (ii) the assumption of no interactions.

- Either problem can give rise to very paradoxical results.

- The causal inference literature has provided alternative counterfactual definitions of direct and indirect effects that generalize those in the social science.

- The causal inference literature has made clear and more precise the no-unmeasured-confounding assumptions required for a causal interpretation.


References

References


Question 1

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<tr>
<th>Individual</th>
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For individuals of type 4, 5 and 6 (1, 2 and 3 were analyzed earlier)

1. Give the outcomes that would have actually occurred if persons of that type were exposed.

2. Give the outcomes that would have actually occurred if persons of that type were unexposed.

3. Calculate (i) the total effect, (ii) both controlled direct effects, (iii) natural direct and indirect effects for individuals of types 4, 5 and 6.
Question 2

Consider the causal diagram below. Suppose data is available on C but not on U.

1. Are the controlled direct effects identified in this causal diagram? Why or why not?

2. Are the natural direct and indirect effects identified in this causal diagram? Why or why not?

3. Could this diagram have come from a trial in which treatment A was randomized within strata of C? Why or why not?
2. Regression Methods for Direct and Indirect Effects
Outline

1. Mediation regression methods for continuous and dichotomous outcomes

2. SAS and STATA macros

3. A Monte Carlo simulation-based method
Under our confounding assumptions (1)-(4), natural direct and indirect effects are given by the following expressions:

\[
NDE = \sum_{m,c} \{E[Y|A = a, m, c] - E[Y|A = a^*, m, c]\} P(M = m|A = a^*, c)P(c)
\]

\[
NIE = \sum_{m,c} E[Y|A = a, m, c]\{P(M = m|A = a, c) - P(M = m|A = a^*, c)\} P(c)
\]

We could consider fitting a parametric regression model for \(Y\) and a parametric regression model for \(M\) and computing this analytically (VanderWeele and Vansteelandt, 2009, 2010; Valeri and VanderWeele, 2013).
Regression methods for causal mediation analysis

- Employ definitions of direct and indirect effects that arise under the counterfactual framework

- Account for the complex nature of the data (interactions, non-linear effects, time to event, spatial and temporal structure)

- Account for pitfalls of observational data (measurement error, missing data, selection bias, confounding)

- Allow assessment of uncertainty
Causal Mediation Analysis in Non-Linear Models

- VanderWeele and Vansteelandt (2009, 2010) and Imai et al. (2010) develop regression approaches allowing for interactions and binary outcome in cohort and case control studies

- VanderWeele (2011) and Lange (2011) consider regression methods for survival outcome

- Valeri and VanderWeele (2013) derive estimators for direct and indirect effects for binary mediators and count outcomes

- Valeri and VanderWeele (2013) develop SAS and SPSS macros that implement mediation analysis automatically and have been translated into STATA (Emsley et al., 2013) and into R (GitHub: causalMediation, under development)

- Other packages for causal mediation analysis in R are mediation and medflex (Imai et al., 2010; Steen et al, 2015)

- All these methods allow for exposure-mediator interactions
Continuous Outcome

Let $Y$ denote the continuous outcome, $M$ the continuous intermediate variables, $A$ the exposure and $C$ additional covariates of interest.

$$E[Y|a, m, c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta'_4 c$$

$$E[M|a, c] = \beta_0 + \beta_1 a + \beta'_2 c$$

Provided that the models are correctly specified and the identification assumptions (i)-(iv) hold, controlled direct effects, natural direct and indirect effects are derived as (VanderWeele and Vansteelandt, 2009):

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

$$NDE = (\theta_1 + \theta_3 \beta_0 + \theta_3 \beta_1 a^* + \theta_3 \beta'_2 C)(a - a^*)$$

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

If the marginal NDE were of interest then we would replace $C$ with $E(C)$. 
Continuous Outcome

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:

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

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

which are the expressions for direct and indirect effects under the product method (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.
Continuous Outcome

With a continuous outcome the "product method" and "difference method" will coincide (MacKinnon et al., 1995)

Thus the traditional epi approach (the "difference method") for a continuous outcome will give valid estimates of direct and indirect effects provided:

(i) the model without the interaction is correctly specified
(ii) the no unmeasured confounding assumptions (1)-(4) are satisfied

Under these assumptions the "difference method" gives natural direct and indirect effects (estimates with a causal interpretation)

We have considered how to handle violations of (i)
With sensitivity analysis we’ll consider how to handle violations of (ii)
Continuous Outcome

As we have already seen the total effect is simply the sum of the natural direct and indirect effects and thus

\[ TE = NDE + NIE \]
\[ = (\theta_1 + \theta_3\beta_0 + \theta_3\beta_1 a^* + \theta_3\beta_2' C)(a - a^*) + (\theta_2\beta_1 + \theta_3\beta_1 a)(a - a^*) \]

Sometimes we are interested in the ”proportion mediated” i.e. the ratio of the indirect effect to the total effect

\[ PM = \frac{NIE}{NDE + NIE} \]

This measure only makes sense if the \( NIE \) and \( NDE \) are in the same direction.
Continuous Outcome

Using the regression models:

\[ E[Y | a, m, c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 a m + \theta_4 c \]

\[ E[M | a, c] = \beta_0 + \beta_1 a + \beta_2 c \]

It is possible to obtain standard errors for these expressions using the delta method, for example:

\[ \text{Var}(CDE) = \sigma_{11}^\theta + 2\sigma_{13}^\theta m + \sigma_{33}^\theta m^2 \]

\[ \text{Var}(NIE) = (\theta_2 + \theta_3 a)(2\sigma_{11}^\theta + \beta_{12}(\sigma_{22}^\beta + 2\sigma_{23}^\theta a + \sigma_{33}^\theta a^2) \]

where \( \sigma_{ij}^\theta \) is the covariance between estimates of \( \theta_i \) and \( \theta_j \) in the regression model for \( Y \) and \( \sigma_{ij}^\beta \) is the covariance between estimates of \( \beta_i \) and \( \beta_j \) in the regression model for \( M \) (these can be obtained from standard regression software)
Definitions: Odds Ratios

For a binary outcome, one could likewise define similar effects on the odds ratio scale (VanderWeele and Vansteelandt, 2010)

Controlled direct effect: The controlled direct effect comparing treatment level \(A = 1\) to \(A = 0\) setting \(M = m\)

\[
CDE^{OR}(m|c) = \frac{P(Y_{1m} = 1|c)/P(Y_{1m} = 0|c)}{P(Y_{0m} = 1|c)/P(Y_{0m} = 0|c)}
\]

Note that this effect is conditional on \(C = c\) not marginalized over it; this will more easily allow us to estimate these effects with regressions

We can give similar definitions for \(NDE\) and \(NIE\) odds ratios
On the odds ratio scale we have: \(TE = NDE \times NIE\)
Binary Outcome

Let $Y$ denote the binary outcome, $M$ the continuous intermediate variables, $A$ the exposure and $C$ additional covariates of interest.

\[
\text{logit}\{P(Y = 1 | a, m, c)\} = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta'_4 c
\]

\[
E[M | a, c] = \beta_0 + \beta_1 a + \beta'_2 c.
\]

Provided that the outcome is rare (or using log linear models instead of a logistic model) and identification assumptions (i)-(iv) hold, we can combine the estimates to get the following formulas for direct and indirect effects (VanderWeele and Vansteelandt, 2010):

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

\[
\log\{OR^{NDE}\} \approx \{\theta_1 + \theta_3 (\beta_0 + \beta_1 a^* + \beta'_2 c + \theta_2 \sigma^2)\}(a - a^*) + 0.5\theta_3^2 \sigma^2 (a^2 - a^{*2})
\]

\[
\log\{OR^{NIE}\} \approx (\theta_2 \beta_1 + \theta_3 \beta_1 a)(a - a^*)
\]

where $\sigma^2$ is the error variance in the linear regression for $M$. 

Binary Outcome

Without interaction ($\theta_3 = 0$) the expressions above reduce to those that can be found in the social science literature ("product method").

i.e. $\theta_1$ for the direct effect
and $\beta_1 \theta_2$ for the mediated effect

With a dichotomous outcome the "product method" and "difference method" do not always give the same estimates (MacKinnon and Dwyer, 1993); neither can in general be interpreted as a natural indirect effect unless the outcome is rare

When the outcome is rare the two methods will be approximately equal (VanderWeele and Vansteelandt, 2010) when there is no interaction and either can be interpreted as a natural indirect effect under no confounding assumptions (1)-(4)
Thus the traditional epi approach (the ”difference method”) for a dichotomous outcome and logistic regression will give valid estimates of direct and indirect effects provided:

(i) the model without the interaction is correctly specified
(ii) the no unmeasured confounding assumptions (1)-(4) are satisfied
(iii) the outcome is rare

Under these assumptions the ”difference method” gives natural direct and direct effect log odds ratios

We can relax (iii) by using log-linear rather than logistic regression

However, if interactions are present and ignored the ”difference method” will give a weighted average of natural indirect effects in which weights do not sum to 1 (Hafeman, 2009)
Binary Outcome

The approach just described would be applicable to cohort data, however a modification is needed for case-control data.

The outcome logistic regression consistently estimates the parameters that would be obtained in a cohort study (except the intercept):

\[
\text{logit}\{P(Y = 1|a, m, c)\} = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4 c
\]

The linear regression for the mediator cannot be applied directly to case-control data, we can run a weighted mediator regression.

Given the prevalence \(\pi\) of the outcome we can obtain the estimates that we would have from a cohort study by weighting cases by \(\pi/p\) and controls by \((1 - \pi)/(1 - p)\) where \(p\) is the proportion of cases in the study (VanderWeele and Vansteelandt, 2010)

\[
E[M|a, c] = \beta_0 + \beta_1 a + \beta_2 c
\]

and robust standard errors need to be used to account for the weighting.
Binary Outcome

Alternatively as an approximation to weighting, if the outcome is rare we could simply fit the model for the mediator amongst the controls

\[ E[M|a, c, Y = 0] = \beta_0 + \beta_1 a + \beta_2' c. \]

Under a rare outcome assumption this would approximate the regression for the mediator in the population

\[ E[M|a, c] = \beta_0 + \beta_1 a + \beta_2' c. \]

This would allow us to proceed even without estimates of the prevalence
Binary Outcome

From the natural direct and indirect effects on the odds ratio scale with rare outcome one can also obtain the proportion mediated on the risk difference scale:

\[ PM = \frac{OR^{NDE} \times (OR^{NIE} - 1)}{(OR^{NDE} \times OR^{NIE} - 1)}. \]

Example: If the unexposed risk is 0.01 with \( NDE = 5 \) and \( NIE = 1.2 \) Then the risk under the \( NDE \) scenario is 0.05 (when you move from \((0, M_0)\) to \((1, M_0)\))
This is elevated to \( 0.05\times1.2 = 0.06 \) when moving up to \((1, M_1)\).
On the risk difference scale there is a \((0.05-0.01) = 0.04\) increase due to the \( NDE \) and a \((0.06-0.05) = 0.01\) increase due to the \( NIE \)
This gives 20% as the proportion mediated i.e. \( (0.01)/(0.01+0.04) = 1/5 \)
The measure above captures this \( PM = 5 \times (1.2-1)/(5 \times 1.2 -1) = 1/5 = 0.20 \)

This measure only makes sense if the \( NIE \) and \( NDE \) are in the same direction
Macros for Mediation Analysis

Macros are currently available that conduct the regression approaches in a variety of softwares:

- **SAS** (covered in lecture, Valeri and VanderWeele, 2013 and 2015)
- **SPSS** (see Valeri and VanderWeele, 2013)
- **Stata** (command is 'paramed')
- Rpackage under development available in GitHub as "CausalMediation"

Macros handle:

- Continuous and Binary Mediators
- Continuous, Binary (Logistic or Log-Linear), Count (Poisson and Negative Binomial), Failure Time Outcomes (Cox, AFT)
- Randomized Trials, Cohort Designs, Unmatched Case-Control Designs
The Stata command "paramed" was developed with Stata version 12.

The "paramed" package can be placed into the user's "ado/plus/p" folder or downloaded using "ssc install paramed."

The command can be used with the following statement:

```
paramed varname, avar() mvar() cvars() a0() a1() m() yreg() mreg()
```
STATA command for mediation

```
paramed varname, avar() mvar() cvars() a0() a1() m() yreg() mreg()
```

With:

- **varname**: is the outcome variable
- **avar()**: is for the exposure variable
- **mvar()**: is for the mediator variable
- **cvars()**: is for the other covariates in the model
- **a0()**: the baseline level of the exposure being compared e.g. 0
- **a1()**: the new exposure level e.g. 1
- **m()**: the level of the mediator at which to compute CDEs
- **yreg()**: the outcome regression model (linear, logistic, log-linear, Poisson or negative binomial)
- **mreg()**: the mediator regression model (linear or logistic)
The option "nointer" exclude an exposure-mediator interaction from the model.

The option "case" is to be specified if the data arise from a case-control study and the outcome is rare and then the mediator regression is run just among the controls.

The option "full" gives a more complete output (including both pure and total natural direct and indirect effects, and conditional along with marginal effects); the values for the covariates at which to compute causal effects conditional on those covariate values must then be entered by also employing the option ?c()”

The option "boot" gives bootstrapped standard errors with 1000 bootstrap replications; to change the number of replications the user can use the option "reps()" and input the number of replications in the parentheses; the option "seed()" can be used with the seed specified in parentheses.

The option "level()” can be used to specify the level at which the confidence interval is calculated.
Statistical vs Counterfactual approach

- For linear and log-linear outcome models, they will coincide when there is no exposure-mediator interaction;

- For logistic outcome models, they will coincide when there is no exposure-mediator interaction and when the outcome is rare.

Thus, before an investigator proceeds with one of the traditional approaches (the product method or difference method) he or she should:

1. Consider whether control has been made for exposure-outcome confounders, mediator-outcome confounders, and exposure-mediator confounders,

2. Check whether there is exposure-mediator interaction, and

3. If the outcome is binary and logistic regression is used, check whether the outcome is rare.
"Pure" versus "Total" Natural Direct and Indirect Effects

We have been considering:

\[ NDE = Y_{1M_0} - Y_{0M_0} \]

\[ NIE = Y_{1M_1} - Y_{1M_0} \]

Robins and Greenland (1992) called the "natural direct and indirect effects" the "pure direct effect" and the "total indirect effect". We could instead consider:

\[ NDE = Y_{1M_1} - Y_{0M_1} \]

\[ NIE = Y_{0M_1} - Y_{0M_0} \]
"Pure" versus "Total" Natural Direct and Indirect Effects

We still have a partitioning of the total effect:

\[ Y_1 - Y_0 = Y_{1M_1} - Y_{0M_0} = (Y_{1M_1} - Y_{0M_1}) + (Y_{0M_1} - Y_{0M_0}) \]

We might call these the "total direct effect" and the "pure indirect effect" "Pure" and "Total" concern how we account for a "mediated interaction".

For continuous outcome and mediator and \( a = 1 \) and \( a^* = 0 \)

\[ TNIE = (\theta_2\beta_1 + \theta_3\beta_1a)(a - a^*) = (\theta_2\beta_1 + \theta_3\beta_11)(1 - 0) \]
\[ PNIE = (\theta_2\beta_1 + \theta_3\beta_1a^*)(a - a^*) = (\theta_2\beta_1 + \theta_3\beta_10)(1 - 0) \]

TNIE gives stronger evidence for the actual operation of mediating pathways (Suzuki et al., 2011; VanderWeele, 2011)
A Monte Carlo Approach

Under our confounding assumptions, natural direct and indirect effects are given by the following expressions:

\[
E[Y_{aM} - Y_{a^* M^*}] = \sum_{m,c} \{E[Y|A = a, m, c] - E[Y|A = a^*, m, c]\} P(M = m|A = a^*, c) P(c)
\]

\[
E[Y_{aM} - Y_{aM^*}] = \sum_{m,c} E[Y|A = a, m, c] \{P(M = m|A = a, c) - P(M = m|A = a^*, c)\} P(c)
\]

We have considered the use of a regression model for Y and a regression model for M to calculate these.

Imai et al. (2010b) instead propose to use parametric or semiparametric models for Y and M and then to use simulations to calculate natural direct and indirect effects using the formulas above and the standard errors for these effects by bootstrapping.
A Monte Carlo Approach

For each bootstrapped sample (a sample from replacement using the original sample) one fits the models for $M$ and $Y$

For each level of treatment $A = a$ and $A = a^*$ one then simulates a value for $M$ and then simulates a value for $Y$ conditional on the value for $M$ and the value for $A$ and then averages over these to get the natural direct and indirect effects

$$E[Y_{aM_{a*}} - Y_{a^*M_{a*}}] = \sum_{m,c} \{E[Y|A = a, m, c] - E[Y|A = a^*, m, c]\} P(M = m|A = a^*, c) P(c)$$

$$E[Y_{aM_a} - Y_{aM_{a*}}] = \sum_{m,c} E[Y|A = a, m, c] \{P(M = m|A = a, c) - P(M = m|A = a^*, c)\} P(c)$$

Confidence intervals are then calculated by e.g. taking the 2.5% and 97.5% quantiles of the NDE and NIE estimates across the bootstrapped samples (Imai et al., 2010b)

Imai et al. (2010c) describes how this can be done automatically using an R package
A Monte Carlo Approach

In the cases we have been considering for a continuous outcome this Monte Carlo approach will give very similar results to the SAS macro.

For the binary outcome case the Monte Carlo approach will calculate the natural direct and indirect effects on the risk difference rather than odds ratio scale.

The Monte Carlo approach is more flexible in that it also handles non-rare outcomes and semi-parametric models for $Y$ and $M$.

The only disadvantages of the approach are (i) computational time and the need to run a new simulation for each two distinct values of treatment and (ii) implementation is currently only available in R.

Otherwise this constitutes a useful and more general alternative approach.
Summary

- If the identification assumptions hold we can estimate natural direct and indirect effects using two regressions and allow for interaction.

- This can be done automatically with SAS, Stata, and SPSS macros.

- This approach will sometimes coincide with but is more general than the product and difference method.

- For a dichotomous outcome, the approach requires either a rare outcome or replacing the logistic regression with a log-linear regression.

- Similar results also hold for a binary mediator.

- A simulation-based approach can be used for additional model flexibility.
References


References


References


3. Sensitivity Analysis for Direct and Indirect Effects
Outline

1. Sensitivity Analysis for Total Effects for Differences

2. Sensitivity Analysis for Ratios

3. Sensitivity Analysis for Controlled Direct Effects

4. Sensitivity Analysis for Natural Direct and Indirect Effects
Unmeasured Confounding

Unmeasured/uncontrolled confounding is a common problem in observational epidemiology

Attempts are made to collect data on and control for as many covariates as possible that are related to the exposure and the outcome of interest

Often, however, one or more important covariates will remain unmeasured that might confound the relationship between the exposure and the outcome

\[ C \rightarrow A \rightarrow Y \]

\[ U \rightarrow A \]
Sensitivity Analysis

Sensitivity analysis techniques can help assess the extent to which an unmeasured variable (or variables) $U$ would have to affect both exposure $A$ and outcome $Y$ in order for the observed associations between $A$ and $Y$ to be attributable solely to confounding rather than a causal effect of $A$ on $Y$.

Sensitivity analysis can also be useful in assessing a plausible range of values for the causal effect of $A$ on $Y$ corresponding to a plausible range of assumptions concerning the relationship between the unmeasured confounder $U$ and the exposure $A$ and outcome $Y$. 
Sensitivity Analysis

A comparison is usually made between our estimate controlling for covariate $C$ and the true causal effect:

$$\{E[Y|a_1, c] - E[Y|a_0, c]\} - \{E[Y_{a_1}|c] - E[Y_{a_0}|c]\}$$

The basic idea is to specify parameters corresponding to the relationships between $U$ and $Y$ and between $U$ and $A$ and then vary these parameters across plausible ranges to see how the "corrected" estimate of the effect varies.

A distinction is sometimes also drawn between:

- "Sensitivity analysis" parameters over plausible range
- "External adjustment" external data is used to set values
Sensitivity Analysis

An early application of this approach was the work of Cornfield et al. (1959) who showed that the association between smoking and lung-cancer association was unlikely to be entirely due to unmeasured confounding by an unknown genetic factor.

The term "sensitivity analysis" is often used outside the context of unmeasured confounding bias.

The term "sensitivity analysis" and a similar approach is often used to address other types of bias such as selection bias and measurement error.

The term "bias analysis" has been used more recently to describe this whole range of techniques.
Sensitivity Analysis

Many sensitivity analysis techniques for unmeasured confounding have been developed.

We will consider an easy-to-use technique under simplifying assumptions.

We will use counterfactual notation.

However the results all essentially just compare:

1. what one obtains adjusting only for measured covariates $C$ with

2. what one would have obtained had it been possible to adjust for measured covariates $C$ and unmeasured covariate(s) $U$

$$\{E[Y|a_1, c] - E[Y|a_0, c]\} - \{E[Y_{a_1}|c] - E[Y_{a_0}|c]\}$$

We also give a very general result encompassing many of the previous sensitivity analysis techniques in the literature.
Sensitivity Analysis

Suppose that the effect of $A$ on $Y$ is unconfounded conditional on $(C, U)$ but not unconfounded given $C$ alone i.e. we have that

$$Y_a \perp A|(C, U)$$

We define the bias factor on the additive scale as the difference between (i) the expected differences in outcomes comparing $A = a_1$ and $A = a_0$ conditional on covariates $C$ and (ii) the true causal effect (i.e. what we would have obtained had we been able to adjust for $U$)

$$B_{add}(c) = \{E[Y|a_1, c] - E[Y|a_0, c]\} - \{E[Y_{a_1}|c] - E[Y_{a_0}|c]\}$$
Sensitivity Analysis

Result. Suppose that we have a binary unmeasured confounder $U$ with the effect of $U$ on $Y$ assumed to be the same in the exposed and unexposed ($\gamma$):

Then the conditional bias is just:

$$B_{add}(c) = \gamma \delta$$

- $\gamma$ is the effect of $U$ on $Y$ i.e. $E[Y|a, U = 1, c] - E[Y|a, U = 0, c]$  
- $\delta$ is the prevalence difference of $U$ between the exposed and unexposed conditional on $C = c$ i.e. $P(U = 1|a_1, c) - P(U = 1|a_0, c)$

Note these parameters are conditional on / control for measured $C$
Once we have calculated the bias term $B_{\text{add}}(c)$ we can simply estimate our causal effect conditional on $C$ and then subtract the bias term to get the "corrected estimate" i.e. what we would have obtained if we had controlled for $C$ and $U$.

To get adjusted confidence intervals on can simply subtract $\gamma\delta$ from both limits of the estimated confidence intervals for either conditional effects or for average causal effects if $B_{\text{add}}(c)$ is constant over $c$. 

---

**Sensitivity Analysis for Total Effects**

- Once we have calculated the bias term $B_{\text{add}}(c)$ we can simply estimate our causal effect conditional on $C$ and then subtract the bias term to get the "corrected estimate" i.e. what we would have obtained if we had controlled for $C$ and $U$.

- To get adjusted confidence intervals on can simply subtract $\gamma\delta$ from both limits of the estimated confidence intervals for either conditional effects or for average causal effects if $B_{\text{add}}(c)$ is constant over $c$. 

---
Sensitivity Analysis for Total Effects

How do we choose sensitivity analysis parameters:

1. See how substantially the confounding would have to be explain away an effect (we could do this for the estimate and CI)
2. Use other studies to inform the parameters
3. Choose something plausible and vary the sensitivity analysis parameters over a range of plausible values
Rosenbaum and Rubin (1983) consider a study comparing coronary artery bypass surgery \((A = 1)\) to medical therapy \((A = 0)\) in the treatment of coronary artery disease.

\(Y\) is symptomatic relief after six months.

Data are available on 74 covariates \((C)\) and they use a propensity-score approach to form five propensity-score subclasses.

The overall adjusted relief rates are 0.67 for surgery and 0.36 for medical therapy.

The estimate of the causal effect is 0.31 (95% CI =0.169 to 0.451).
Sensitivity Analysis Example

Using the simple sensitivity-analysis technique described above, we see that, if there were a binary unmeasured confounding variable $U$ with a 0.6 higher prevalence among those with surgery versus medical therapy

$$\delta = 0.6$$

and if the outcome difference comparing $U = 1$ and $U = 0$ were 0.517 for both treatment groups in all propensity-score strata,

$$\gamma = 0.51$$

then we would obtain a bias term of $B_{\text{add}} = (0.517)(0.6) = 0.31$.

Such an unmeasured confounding variable would reduce the estimate of the causal effect to 0 (95% CI =-0.141 to 0.141).
Sensitivity Analysis Example

It seems unlikely that an unmeasured confounding variable could have an effect on the outcome sufficiently large (even after control for 74 covariates) to invalidate the qualitative conclusion of surgery providing higher proportion of relief at six months than medical therapy.

If we changed the effect of $U$ to be 0.25 then we would obtain a bias term of $B_{add} = (0.25)(0.6) = 0.15$ and our estimate of the causal effect would still be $0.31 - 0.15 = 0.16$ (95% CI $= 0.019$ to 0.301).

A 60 percentage point difference in the prevalence of the unmeasured confounder would be inadequate to explain away the estimated effect, even if the unmeasured confounder had an effect of magnitude, 0.25, which is still quite large.
Sensitivity Analysis

The simplified result $B_{add}(c) = \gamma \delta$ was reported in several papers (e.g. Lin et al., 1998) but only for certain cases: e.g. Using regression with no interaction b/w treatment and covariates.

In fact it can be shown to work (VanderWeele and Arah, 2011) irrespective of the method employed to estimate effects: Regression, propensity score, IPW, doubly robust methods, etc.

It only requires the effect of $U$ on $Y$ is the same of the exposed and unexposed.
Sensitivity Analysis Extensions

- If $U$ is assumed continuous then we can instead let $\delta$ be the difference in expectation of $\{E(U|A = 1) - E(U|A = 0)\}$

- If the bias parameters are specified as the same for all strata of $C$ then the same approach (calculating $B_{add}(c) = \gamma \delta$ and subtracting this from the estimate and both limits of the confidence interval) still applies.

$$B_{add}(c) = \sum_c \{E[Y|a_1, c] - E[Y|a_0, c]\} p(c) - \{E[Y_{a_1}] - E[Y_{a_0}]\}$$
Sensitivity Analysis Extensions

- We can also specify different sensitivity parameters for different covariate strata; for each $C$ we could calculate

$$B_{add}(c) = \gamma \delta_c$$

where $\gamma$ is the effect of $U$ on $Y$ and $\delta_c$ is the prevalence difference of $U$ between the exposed and unexposed for that strata of $C = c$

- We could combine across strata by averaging the bias factor over $C$:

$$B_{add} = \sum_c B_{add}(c)p(c)$$

If the effect of $U$ also does not interact with $C$ we can apply the result immediately (without averaging) to the overall causal effect

we interpret $\gamma$ as the effect of $U$ on $Y$ and $\delta$ is the overall prevalence difference of $U$ between the exposed and unexposed
Sensitivity Analysis Extensions

- Once we have calculated the overall bias term $B_{add}$ we can simply estimate our causal effect controlled or adjusted for only using $C$ and then subtract the bias term to get the ”corrected estimate” i.e. what we would have obtained if we had controlled/adjusted for $C$ and $U$

- We can only simply subtract $\gamma \delta$ from both limits of the estimated confidence intervals for either conditional effects or for average causal effects if $B_{add}(c)$ is constant over $c$

- To get adjusted confidence intervals for the average causal effect when $B_{add}(c)$ is not constant over $c$ and one must use

$$B_{add} = \sum_c B_{add}(c)p(c)$$

in which case there is variability due to estimating $P(C = c)$ and to get the adjusted confidence intervals one could use bootstrapping.
Sensitivity Analysis Extensions

- We can also relax the assumption that the effect of $U$ on $Y$ are the same for the exposed and the unexposed (VanderWeele and Arah, 2011) but this then requires more sensitivity analysis parameters.

- In general there is tension between a sensitivity analysis that is (i) simple and easier to use without requiring too many parameters and one that is (ii) general without making many assumptions.

- In observational epidemiology, unmeasured confounding is frequently a problem and at least the simple approach described above should be considered.

If the effect can be explained away with the simple approach then it can be explained away with a more nuanced one as well.
Sensitivity Analysis for Risk Ratios

Thus far we have considered risk differences or average expected outcome differences.

For a binary outcome a similar approach could be used for risk ratios and odds ratio.

A very general approach is possible (VanderWeele and Arah, 2011) but we’ll focus here on an easy to use approach under simplifying assumptions which is applicable with risk ratios (or with odds ratio with a rare outcome).

The multiplicative bias term for the causal risk ratio is the estimate of the risk ratio controlling for C (but not U) divided by the true causal risk ratio conditional on C (had we been able to adjust for U):

\[
B_{\text{mult}}(c) = \frac{E[Y|a_1, c]/E[Y|a_0, c]}{E[Y_{a_1}|c]/E[Y_{a_0}|c]}
\]
Sensitivity Analysis

Result. If there is no unmeasured confounding given \((C, U)\) i.e. 
\(Y_a \perp A|(C, U)\) and \(U\) is a binary unmeasured confounder with the same 
effect, \(\gamma\), on \(Y\) for both exposed and unexposed so that  
(Schlesselman,1978)

\[
\gamma = \frac{E[Y|a, c, U = 1]}{E[Y|a, c, U = 0]}
\]

We have that:

\[
B_{mult}(c) = \frac{1 + (\gamma - 1)P(U = 1|a_1, c)}{1 + (\gamma - 1)P(U = 1|a_0, c)}
\]

We can use the bias formula by specifying:

- \(\gamma\) = the effect of \(U\) and
- the prevalence of \(U\) amongst the exposed and unexposed

We can estimate the risk ratio controlling only for \(C\) and we divide our 
estimate by \(B_{mult}(c)\) to get the corrected estimate for the causal risk 
ratio i.e. what we would have obtained if we had adjusted for \(U\) also
Moorman et al. (2008) report on associations between ovarian cancer and breast-feeding

For premenopausal women, with no breast-feeding as a reference group they find odds ratio for ovarian cancer of:

- <6 months, 0.8 (95% CI: 0.5, 1.2)
- 6-12 months, 0.5 (95% CI: 0.3, 0.8)
- >12 months, 0.3 (95% CI: 0.1, 0.9)

Moorman et al. (2008) control for a number of covariates but do not control for SES

Let $U = 1$ denote low (versus high reference) SES. We might think e.g. the 6-12 months OR of 0.5 (95% CI: 0.3, 0.8) is confounded
Sensitivity Analysis Example

We might think e.g. the 6-12 months OR of 0.5 (95% CI: 0.3, 0.8) is confounded

Suppose we thought that low SES increased the risk of ovarian cancer by 1.5 fold and that 30% of the 6-12 month breastfeeding group was low SES but 70% of the reference group (no breast-feeding) was low SES

The bias factor is then:

\[
\frac{1 + (1.5 - 1) \times (0.3)}{1 + (1.5 - 1) \times (0.7)} = 0.85
\]

The corrected estimate would be 0.6 (95% CI: 0.4, 0.9)
Sensitivity Analysis Example

Suppose we thought that low SES increased the risk of ovarian cancer by 2.5 fold and that 30% of the 6-12 month breastfeeding group was low SES but 70% of the reference group (no breast-feeding) was low SES.

The bias factor is then:

\[
\frac{1 + (2.5 - 1) \times (0.3)}{1 + (2.5 - 1) \times (0.7)} = 0.71
\]

The corrected estimate would be 0.7 (95% CI: 0.4, 1.1).

The estimate is still protective but the confidence interval now does not contain 1.

Fairly substantial confounding would require to completely explain away the effect, but the initial estimate may indeed be an exaggerated estimate.
Approaches to Sensitivity Analysis

Sensitivity analysis does not give one right answer but a range

It is sometimes objected that there is too much subjectivity in using sensitivity analysis

Possible Approaches:

1. Report how large the effects of the confounder would have to be to completely explain away the effect

2. Find the most important measured confounder variable; examine if an unmeasured confounder of similar strength would change conclusions

3. Create a table with many values of all sensitivity analysis parameters; include those one thinks are too extreme; let the reader decide

4. Use external data or expert opinion to inform sensitivity analysis parameters
Approaches to Sensitivity Analysis

Note that: Approaches (1)-(3) do not require knowledge of what the unmeasured confounder is.

They can be used even if the investigators have seemingly controlled for everything imaginable.

Sometimes the choice of sensitivity analysis will depend on audience.

Epidemiologic journals are likely to welcome a more thorough sensitivity analysis with a large table.

With medical journals at least reporting (i) the degree of unmeasured confounding required to explain away the estimate and (ii) the corrected estimate obtained under what is thought to be a plausible scenario is feasible and helpful.
Sensitivity Analysis for CDEs

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 start considering a technique for CDEs under simplifying assumptions.
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.

Suppose we fit a logistic regression adjusted only for \(C\):

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

The CDE effect of the exposure \(A\) controlling for \(M\) is \(\exp(\theta_1 + \theta_3 m)\)

e.g. if \(M\) is binary then we have ”direct effects” of
\(CDE(m = 0) = \exp(\theta_1)\)
\(CDE(m = 1) = \exp(\theta_1 + \theta_3)\)

However, if we have not adjusted for \(U\) this will be biased.
Sensitivity Analysis

Let $B$ denote the ratio between (i) the estimate and (ii) what would have been obtained had we adjusted for $U$ as well

$$B = \frac{E[Y|a, m, c]/E[Y|a^*, m, c]}{E[Y_{am}|c]/E[Y_{a^*m}|c]}$$

Suppose that $U$ were binary and had a constant effect $\gamma$ on $Y$ across exposure groups on the risk ratio scale:

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

Result. The bias factor is equal to (VanderWeele, 2010)

$$B_{mult}(c) = \frac{1 + (\gamma - 1)P(U = 1|a, m, c)}{1 + (\gamma - 1)P(U = 1|a^*, m, c)}$$
The approach can be used to resolve the birthweight paradox.

The odds of infant mortality amongst infants <2000g is 0.79 lower for smoking mothers than non-smoking mothers.

$$CDE(m = 1) = 0.79$$

If $U$ denotes a common cause of low birthweight and infant mortality (e.g. birth defect / malnutrition) then...
Birthweight Paradox

If the effect of \( U \) increases the risk of infant mortality 3.5 fold and

\[
\gamma = 3.5
\]

If the prevalence of \( U \) for low-birth weight infants whose mothers smoke is 0.025 but the prevalence of \( U \) for low-birth weight infants whose mothers do not smoke is 0.14 (smoking is ruled out as an explanation of LBW rendering other causes more likely)

\[
P(U = 1|a = 1, m, c) = P(U = 1|a = 1, 1, c) = 0.025 \\
P(U = 1|a = 0, m, c) = P(U = 1|a = 0, 1, c) = 0.14
\]

\[
Bias(CDE) = \frac{1 + (3.5 - 1) \times 0.025}{1 + (3.5 - 1) \times 0.14} = 0.79
\]

And our corrected estimate would be \( 0.79/Bias(CDE) = 0.79/0.79 = 1 \)
and such confounding would completely explain away the paradox
Sensitivity Analysis for CDEs

A similar approach also works for CDEs on the difference scale

Let $B$ denote the difference between estimated CDE conditional on $C$ and the true controlled direct effect conditional on $C$ (what would have been obtained had we been able to adjust for $U$ as well)

$$B = \{E[Y|a, m, c] - E[Y|a^*, m, c]\} - \{E[Y_{am}|c] - E[Y_{a^*m}|c]\}$$

General non-parametric expressions for the Bias term for the CDE are available (VanderWeele, 2010)

We’ll again consider a simplified approach
Sensitivity Analysis for CDEs

Result. Suppose that no-confounding assumptions (1) and (2) hold for 
\((C, U)\) where \(U\) is binary

i.e. \(Y_{am} \perp A|(C, U)\) and \(Y_{am} \perp M|(C, U, A)\)

then if the effect of \(U\) on \(Y\) is constant over \(a\), and if we let

\[
\gamma = E[Y|a, m, c, U = 1] - E[Y|a, m, c, U = 0]
\]
\[
\delta = P(U = 1|a, m, c) - P(U = 1|a^*, m, c)
\]

Then (VanderWeele, 2010):

\[
B = \delta m \gamma m
\]

We can use the bias formula by specifying:

- \(\gamma\) = the risk difference relating \(U\) and \(Y\), conditional on \(A, M, C\)
- the prevalence difference of \(U\) for the exposed vs. unexposed
Sensitivity Analysis for CDEs

We can obtain an estimate of the CDE controlling only for $C$ (e.g. fit a regression of $Y$ on $A, M, C$) and we subtract the bias from our regression estimate to get the corrected estimate for the controlled direct effect i.e. what we would have obtained if we had adjusted for $U$ also.

For conditional controlled direct effects, we can obtain corrected CI by subtracting the bias from both limits of the confidence interval.

The bias formulae for the ratio scale and the difference scale apply also to the hazard ratio scale (VanderWeele, 2011) and the hazard difference (Lange and Hansen, 2011) scales.
Sensitivity Analysis for Natural Direct and Indirect Effects

We will now consider natural direct and indirect effects in a setting in which there is an unmeasured confounder that may affect the mediator and the outcome.

The relationships between \( C \) and \( U \) may be arbitrary.

We assume that no-unmeasured-confounding assumptions (1)-(4) hold conditional on \((C, U)\) but not conditional on \(C\) alone.
Sensitivity Analysis for Natural Direct and Indirect Effects

Very general non-parametric sensitivity analysis techniques for natural direct and indirect effects that can be applied to any statistical estimation method are available (VanderWeele, 2010)

However these require specifying a large number of sensitivity analysis techniques and are not easy to use in practice

1. If there is no exposure-mediator interaction we could use the CDE techniques

2. Imai et al. (2010) has developed an approach for natural direct and indirect effects that is fairly easy to implement using an R program but the interpretation of the sensitivity analysis parameters is not very intuitive

3. Here we will consider one easier-to-use approach that can be applied when both the mediator and the outcome are binary
1. If there is no exposure-mediator interaction we could use the $CDE$ techniques because $NDE$’s equal $CDE$’s

$$B = \delta_m \gamma_m$$

We could subtract our $CDE$ bias formula from the $NDE$ and its confidence interval.

Since $U$ is a confounder of $M - Y$ relationship, the total effect can be validly estimated.

By the property of effect decomposition: $NIE = TE - NDE$

Alternatively, we could add this bias factor to the $NIE$ and its CI
2. Imai et al. (2010) give an approach for natural direct and indirect effects that is fairly easy to implement;

It is possibly the most useful approach in the presence of interaction.

The interpretation of the sensitivity analysis parameters is not as intuitive and is restricted to unmeasured variables that affect only the mediator and the outcome.
An unmeasured confounder of the mediator-outcome relationship will induce correlation between the error terms in regression (2) and (3), 
\[ \rho = \text{Corr}(e_2, e_3) \]

1. \[ Y = \phi_0 + \phi_1 a + \phi_2 c + e_1 \] (1)
2. \[ M = \beta_0 + \beta_1 a + \beta_2 c + e_2 \] (2)
3. \[ Y = \theta_0 + \theta_1 a + \theta_2 m + \theta_4 c + e_3 \] (3)

Imai et al. (2010) show that

\[ TNIE = \frac{\beta_1 \sigma_1}{\sigma_2 (\rho^* - \rho \sqrt{(1 - \rho^2)/(1 - \rho^2)})} \]
\[ \sigma_1 = \text{Var}(e_1|A = 1) \]
\[ \sigma_2 = \text{Var}(e_2|A = 1) \]
\[ \rho^* = \text{Corr}(e_1, e_2|A = 1) \]
The parameters $\sigma_1, \sigma_2, \rho^*$ can be estimated from observed data.

$\rho$ can be set as a sensitivity analysis parameter to examine how strongly the errors $e_2$ and $e_3$ have to be correlated to completely explain away the indirect effect.

Imai et al (2010) provide a software implement for this approach for continuous and binary outcomes (using a probit model).
3. We will consider one easier-to-use approach that can be applied when both the mediator and the outcome are binary and there is an A-M interaction.

Suppose we had a binary outcome and binary mediator:

\[
\begin{align*}
\logit[P(Y = 1|A = a, M = m, C = c)] &= \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4 c \\
\logit[P(M = 1|A = a, C = c)] &= \beta_0 + \beta_1 a + \beta_2 c
\end{align*}
\]
If controlling for C sufficed to control for confounding i.e. suffice to satisfy assumptions (1)-(4) then we would have (Valeri and VanderWeele, 2013):

\[
OR^{CDE}(m) = \exp\{(\theta_1 + \theta_3 m)(a - a^*)\}
\]

\[
OR^{NDE} = \frac{\exp(\theta_1 a)\{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta_2 c)\}}{\exp(\theta_1 a^*)\{1 + \exp(\theta_2 + \theta_3 a^* + \beta_0 + \beta_1 a^* + \beta_2 c)\}}
\]

\[
OR^{NIE} = \frac{\{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c)\}\{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a + \beta_2 c)\}}{\{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c)\}\{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta_2 c)\}}
\]
Sensitivity Analysis for Natural Direct and Indirect Effects

Suppose now that there were an unmeasured binary confounding variable $U$ for the mediator-outcome relationships where we specify (i) the risk ratio $\gamma$ relating $U$ and $Y$ constant across strata of $A$ and $M$; (ii) the prevalence of $U$ in each exposure-mediator stratum, $P(U|A = a, M = m, c)$ so that:

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

$$
B_0 = \frac{1 + (\gamma - 1)P(U = 1|a, M = 0, c)}{1 + (\gamma - 1)P(U = 1|a^*, M = 0, c)}
$$

$$
B_1 = \frac{1 + (\gamma - 1)P(U = 1|a, M = 1, c)}{1 + (\gamma - 1)P(U = 1|a^*, M = 1, c)}
$$

$$
B_2 = \frac{1 + (\gamma - 1)P(U = 1|a^*, M = 1, c)}{1 + (\gamma - 1)P(U = 1|a^*, M = 0, c)}
$$

From (i) and (ii) we can calculate $B_0$, $B_1$ and $B_2$. 
Sensitivity Analysis for Natural Direct and Indirect Effects

If we let

\[ \theta_1^\dagger = \theta_1 - \log(B_0) \]

\[ \theta_2^\dagger = \theta_2 - \log(B_2) \]

\[ \theta_3^\dagger = \theta_3 - \log(B_1) + \log(B_0) \]

And we replace \((\theta_1, \theta_2, \theta_3)\) by \((\theta_1^\dagger, \theta_2^\dagger, \theta_3^\dagger)\) in the original formulas

\[ OR^{CDE}(m) = \exp\{(\theta_1 + \theta_3 m)(a - a^*)\} \]

\[ OR^{NDE} = \frac{\exp(\theta_1 a)\{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta_2 c)\}}{\exp(\theta_1 a^*)\{1 + \exp(\theta_2 + \theta_3 a^* + \beta_0 + \beta_1 a^* + \beta_2 c)\}} \]

\[ OR^{NIE} = \frac{\{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c)\}\{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a + \beta_2 c)\}}{\{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c)\}\{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta_2 c)\}} \]
Sensitivity Analysis for Natural Direct and Indirect Effects

We can assess the sensitivity of the conclusions to unmeasured confounding by varying:

- $\gamma$, the risk ratio relating $U$ and $Y$ and
- the prevalence of $U$ in each treatment-mediator stratum to get:

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

$$
B_0 = \frac{1 + (\gamma - 1)P(U = 1|a, M = 0, c)}{1 + (\gamma - 1)P(U = 1|a^*, M = 0, c)}
$$

$$
B_1 = \frac{1 + (\gamma - 1)P(U = 1|a, M = 1, c)}{1 + (\gamma - 1)P(U = 1|a^*, M = 1, c)}
$$

$$
B_2 = \frac{1 + (\gamma - 1)P(U = 1|a^*, M = 1, c)}{1 + (\gamma - 1)P(U = 1|a^*, M = 0, c)}
$$

and then $(\theta_1^\dagger, \theta_2^\dagger, \theta_3^\dagger)$ and the corresponding effect estimates.

Standard errors can be calculated using the delta method and the relations between the estimated and adjusted coefficients.
Placental Abruption

Placental abruption increases the likelihood of perinatal mortality by about 15-fold. We might consider the extent to which the effect are mediated by preterm delivery and the extent to which they are through other pathways.

We consider outcomes of stillbirth, early neonatal mortality (<7 days), late neonatal mortality (7-28 days) and perinatal mortality (still birth + early)

Placental Abruption

<table>
<thead>
<tr>
<th>Perinatal outcome</th>
<th>Natural direct effect</th>
<th>Natural indirect effect</th>
<th>Total effect</th>
<th>Mortality proportion mediated through preterm delivery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>13.07 (12.49-13.68)</td>
<td>1.29 (1.27-1.32)</td>
<td>16.91 (16.45-17.36)</td>
<td>24.1</td>
</tr>
<tr>
<td>Early neonatal mortality</td>
<td>5.59 (5.19-6.02)</td>
<td>1.61 (1.55-1.67)</td>
<td>8.98 (8.58-9.37)</td>
<td>42.5</td>
</tr>
<tr>
<td>Late neonatal mortality</td>
<td>3.28 (2.90-3.71)</td>
<td>1.79 (1.67-1.91)</td>
<td>5.86 (5.44-6.28)</td>
<td>53.1</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>10.18 (9.80-10.58)</td>
<td>1.35 (1.33-1.38)</td>
<td>13.76 (13.45-14.08)</td>
<td>28.1</td>
</tr>
</tbody>
</table>
Placental Abruption

We could consider how the estimates would be affected by an unmeasured common cause of preterm delivery and the mortality outcome (Ananth and VanderWeele, 2011)

Suppose the prevalence of $U$ amongst term pregnancies was 5% with and without abruption and that the prevalence of $U$ was 10% amongst preterm deliveries with abruption but 50% amongst preterm deliveries without abruption; consider $\gamma = 1.5$ and $\gamma = 6$ for the effect of $U$
Placental Abruption

The estimates do change fairly substantially especially under the severe unmeasured confounding scenario (NDEs were underestimated and NIEs were overestimated) but the conclusions of (i) the majority being direct (through pathways other than preterm delivery) but (ii) there still being a substantial mediated effect, remain even under the severe unmeasured confounding scenario.

<table>
<thead>
<tr>
<th>Perinatal outcome</th>
<th>Observed analysis (no unobserved confounding)</th>
<th>Moderate unobserved confounding (RR_U=1.5)</th>
<th>Severe unobserved confounding (RR_U=6.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$RR_{NDE}$</td>
<td>$RR_{NIE}$</td>
<td>Mort$_{GA}$%</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>13.07</td>
<td>1.29</td>
<td>24.1</td>
</tr>
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<td>10.18</td>
<td>1.35</td>
<td>28.1</td>
</tr>
</tbody>
</table>
Conclusions

- Sensitivity analysis can be useful in assessing the extent to which unmeasured confounding might explain away an estimate. A variety of parameter values can be considered to assess a range of plausible settings.

- With direct and indirect effects, unmeasured confounding variables affecting any of the relationships between the exposure, mediator, and outcome need to be considered.

- Methods for controlled direct effects are reasonably straightforward to implement by hand.

- Methods for natural direct and indirect effect will eventually be implementable by the macro but not yet.

- Bross, I. D. Spurious effects from an extraneous variable. Journal of Chronic Diseases, 1966; 19, 637-647.


References


References


References

References


4. Mediation and Interaction: An Application
Outline

1. A Unification of Mediation and Interaction
2. Regression Approaches
3. Relation to Prior Decompositions
4. Stata Macro for Effect Decomposition
5. Application to Genetic Epidemiology
6. Concluding Remarks
Unification of Mediation and Interaction

We can in fact decompose a total effect, \( TE = Y_1 - Y_0 \), into four components (VanderWeele, 2014):

\[
Y_1 - Y_0 = (Y_{10} - Y_{00}) + (Y_{11} - Y_{10} - Y_{01} + Y_{00})(M_0) + (Y_{11} - Y_{10} - Y_{01} + Y_{00})(M_1 - M_0) + (Y_{01} - Y_{00})(M_1 - M_0)
\]

(1) A controlled direct effect (CDE): the effect of A in the absence of M
(2) A reference interaction (INTref): The interaction if that operates only if the mediator is present in the absence of exposure
(3) A mediated interaction (INTmed): The interaction if that operates only if the exposure changes the mediator
(4) A pure indirect effect (PIE): The effect of the mediator in the absence of the exposure times the effect of the exposure on the mediator
Unification of Mediation and Interaction

Table: Decomposition of the total effect in the presence of exposure-mediator interaction

<table>
<thead>
<tr>
<th>Component</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Direct Effect (CDE)</td>
<td>([Y_{10} - Y_{00}])</td>
</tr>
<tr>
<td>Pure Natural Direct Effect (PNIE)</td>
<td>([Y_{01} - Y_{00}][M_1 - M_0])</td>
</tr>
<tr>
<td>Reference Interaction (INT_ref)</td>
<td>([Y_{11} - Y_{10} - Y_{01} + Y_{00}][M_0])</td>
</tr>
<tr>
<td>Mediated Interaction (INT_med)</td>
<td>([Y_{11} - Y_{10} - Y_{01} + Y_{00}][M_1 - M_0])</td>
</tr>
</tbody>
</table>

\(M_1 = 1[M_1 = m], \ M_0 = 1[M_0 = m]\)

(1) CDE: Neither mediation nor interaction

(1) INTref: Interaction but not mediation

(1) INTmed: Both mediation and interaction

(1) PIE: Mediation but not interaction
Unification of Mediation and Interaction

We cannot identify these effects for an individual but, under certain confounding assumptions (next slides), we can identify them on average for a population:

Table: Decomposition of the total effect in the presence of exposure-mediator interaction

<table>
<thead>
<tr>
<th>Component</th>
<th>Average Causal Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E[CDE]$</td>
<td>$p_{10} - p_{00}$</td>
</tr>
<tr>
<td>$E[INTref]$</td>
<td>$[p_{11} - p_{10} - p_{01} + p_{00}]P(M = 1</td>
</tr>
<tr>
<td>$E[INTmed]$</td>
<td>$[p_{11} - p_{10} - p_{01} + p_{00}][P(M = 1</td>
</tr>
<tr>
<td>$E[PNIE]$</td>
<td>$[p_{01} - p_{00}][P(M = 1</td>
</tr>
</tbody>
</table>

$p_{10} = p_{a=1,m=0} = P(Y = 1|A = 1, M = 1)$

We could calculate the proportions due to each of the components:

$\frac{E[CDE]}{E[TE]}, \frac{E[INTref]}{E[TE]}, \frac{E[INTmed]}{E[TE]}, \frac{E[PNIE]}{E[TE]}.$
Unification of Mediation and Interaction

The four components are:

\[ E[CDE] = p_{10} - p_{00} \]
\[ E[INTref] = [p_{11} - p_{10} - p_{01} + p_{00}]P(M = 1|A = 0) \]
\[ E[INTmed] = [p_{11} - p_{10} - p_{01} + p_{00}][P(M = 1|A = 1) - P(M = 1|A = 0)] \]
\[ E[PNIE] = [p_{01} - p_{00}][P(M = 1|A = 1) - P(M = 1|A = 0)] \]

We could add \( E[INTref] \) and \( E[INTmed] \) for the overall proportion due to interaction:

\[ \frac{E[INTref] + E[INTmed]}{E[TE]} \]

We could add \( E[PIE] \) and \( E[INTmed] \) for the overall proportion due to mediation:

\[ \frac{E[PNIE] + E[INTmed]}{E[TE]} \]
Often in epidemiology, risk ratios or odds ratios are used for convenience or ease of interpretation or to account for study design. By dividing the decomposition by \( p_{a=0} \), we can rewrite this decomposition on the ratio scale as:

\[
RR_{a=1} - 1 = k(RR_{10} - 1) \\
+ k(RR_{11} - RR_{10} - RR_{01} + 1)P(M = 1|A = 0) \\
+ k(RR_{11} - RR_{10} - RR_{01} + 1)\{P(M = 1|A = 1) - P(M = 1|A = 0)\}
\]

where \( k \) is a scaling factor that is given by \( k = \frac{p_{00}}{p_{a=0}} \).
The proportion of the effect attributable to each of the 4 components is given by the expressions below:

\[
P_{ACDE} = \frac{(RR_{10} - 1)}{(RR_{10} - 1) + (RERI)P(M = 1|A = 1) + (RR_{01} - 1)[P(M = 1|A = 1) - P(M = 1|A = 0)]}
\]

\[
P_{INTref} = \frac{(RERI)P(M = 1|A = 0)}{(RR_{10} - 1) + (RERI)P(M = 1|A = 1) + (RR_{01} - 1)[P(M = 1|A = 1) - P(M = 1|A = 0)]}
\]

\[
P_{INTmed} = \frac{(RERI)[P(M = 1|A = 1) - P(M = 1|A = 0)]}{(RR_{10} - 1) + (RERI)P(M = 1|A = 1) + (RR_{01} - 1)[P(M = 1|A = 1) - P(M = 1|A = 0)]}
\]

\[
P_{PIE} = \frac{(RR_{01} - 1)[P(M = 1|A = 1) - P(M = 1|A = 0)]}{(RR_{10} - 1) + (RERI)P(M = 1|A = 1) + (RR_{01} - 1)[P(M = 1|A = 1) - P(M = 1|A = 0)]}
\]
Unification of Mediation and Interaction

The confounding assumptions are the same as those to identify natural direct and indirect effects

1. There are no unmeasured exposure-outcome confounders given $C$
2. There are no unmeasured mediator-outcome confounders given $(C, A)$
3. There are no unmeasured exposure-mediator confounders given $C$
4. There is no effect of exposure that confounds the mediator-outcome relationship

For controlled direct effects, only assumptions (1) and (2) are needed

Note (1) and (3) are guaranteed when treatment is randomized
Unification of Mediation and Interaction

Consider continuous \( Y \) and \( M \).

Under the confounding assumptions we can estimate each of the four components in a straightforward way using regression models for \( Y \) and \( M \):

\[
E[Y|a, m, c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4 c
\]

\[
E[M|a, c] = \beta_0 + \beta_1 a + \beta_2 c
\]

Under these models if our confounding assumptions, then the effects for a change in the exposure from reference level \( a^* \) to level \( a \) are given by:

\[
E[CDE] = \theta_1(a - a^*)
\]

\[
E[INTref] = \theta_3(\beta_0 + \beta_1 a^* + \beta_2 C)(a - a^*)
\]

\[
E[INTmed] = (\theta_3 \beta_1)(a - a^*)(a - a^*)
\]

\[
PNIE = (\theta_2 \beta_1)(a - a^*)
\]
Relation to Decompositions

We can summarize the relations with prior decompositions in a figure:
MED4WAY: A STATA Command for Effect Decomposition

- **med4way** uses parametric regression models to estimate the components of the 4-way decomposition of the total effect of a treatment on an outcome in the presence of a mediator with which the exposure may interact.

- This decomposition breaks down the total effect of the treatment on the outcome into components due to mediation alone, to interaction alone, to both mediation and interaction, and to neither mediation nor interaction.

- **med4way** provides standard errors and confidence intervals for the estimated components using the delta method (default) or the bootstrap. med4way allows continuous, binary, count or survival outcomes, and continuous or binary mediators.
MED4WAY: Installation

To install the current version of **med4way** directly from GitHub in Stata (version 13+), run:

```stata
net install med4way, from("https://raw.githubusercontent.com/anddis/med4way/master/")
```
MED4WAY: Installation

For older versions of Stata, download and extract the zip file and then run:

```
net install med4way, from(mydir)
```

from within Stata, where mydir is the directory that contains the extracted files.
After installation, see the help file:

```
help med4way
```
**Syntax**

```bash
med4way [yvar] avar mvar [cvars] [if] [in], a0(#) a1(#) m(#) yreg(string) mreg(string) [c(string) casecontrol fulloutput nodeltamethod robust level(#) bootstrap reps(#) seed(#) saving(filename, ...)]
```

*yvar* is the variable name for the outcome. Note that *yvar* must not be specified when the model for the outcome is an Accelerated Failure Time or a Cox proportional hazards model. In these cases, you must *stset* your data before running *med4way*.

*avar* is the variable name for the treatment. If binary, it must be coded as 0/1.

*mvar* is the variable name for the mediator. If binary, it must be coded as 0/1.

*cvars* are the variable names for the covariates to be included in the model for the outcome and for the mediator.
### MED4WAY: Options

<table>
<thead>
<tr>
<th>options</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>* a₀(#)</td>
<td>referent treatment level</td>
</tr>
<tr>
<td>* a₁(#)</td>
<td>actual treatment level</td>
</tr>
<tr>
<td>* m(#)</td>
<td>level of the mediator at which to compute the 4-way decomposition</td>
</tr>
<tr>
<td>* yreg(string)</td>
<td>form of the regression model for the outcome</td>
</tr>
<tr>
<td>* mreg(string)</td>
<td>form of the regression model for the mediator</td>
</tr>
<tr>
<td>c(numlist)</td>
<td>values of the covariates cvars at which to compute the 4-way decomposition</td>
</tr>
<tr>
<td>casecontrol</td>
<td>treat the data as coming from a case-control study</td>
</tr>
<tr>
<td>fulloutput</td>
<td>compute also the proportion of the Total Effect attributable to its 4</td>
</tr>
<tr>
<td></td>
<td>components and the proportions attributable to mediation, interaction,</td>
</tr>
<tr>
<td></td>
<td>and either mediation or interaction or both</td>
</tr>
<tr>
<td>nodeltamethod</td>
<td>suppress the calculation of the standard errors using the delta method</td>
</tr>
<tr>
<td>robust</td>
<td>use the sandwich/robust estimator of variance when using a Poisson model</td>
</tr>
<tr>
<td>level(#)</td>
<td>set confidence level; default is level(95)</td>
</tr>
</tbody>
</table>
MED4WAY: Options

casecontrol
  to compute the 4-way decomposition
treat the data as coming from a
case-control study

fulloutput
  compute also the proportion of the Total
  Effect attributable to its 4
  components and the proportions
  attributable to mediation,
  interaction, and either mediation or
  interaction or both

nodeltamethod
  suppress the calculation of the standard
  errors using the delta method

robust
  use the sandwich/robust estimator of
  variance when using a Poisson model
  for the outcome

level(#)  
set confidence level; default is
  level(95)

bootstrap
  use bootstrap to calculate confidence
  intervals

reps(#)
  perform # bootstrap replications;
  default is reps(1000)

seed(#)
  set random-number seed to #

saving(filename, ...)
  save results to filename; save
  statistics in double precision; save
  results to filename every #
  replications

* are required.
Remarks

(1) The four-way decomposition makes clear what proportion of an effect is due (i) to just mediation, (ii) to just interaction, (iii) to both and (iv) to neither

(2) It unites, within a single framework, prior decompositions for mediation and prior decompositions for interaction

(3) It gives the most insight into both phenomena of mediation and interaction

(4) It is relatively straightforward to implement with SAS or Stata code

(5) Sensitivity analysis for measurement error and unmeasured confounding are available for some mediation and interaction measures
Genetic Epidemiology Example

- In 2008, GWAS studies found variants 15q25.1 associated with lung cancer (Thorgeirsson et al., 2008; Hung et al., 2008; Amos et al., 2008)

- These same variant were known to be associated with smoking (average cigarettes per day) (Saccone et al., 2007; Spitz et al., 2008)

- The variants also increased vulnerability to the harmful effect of smoking, a gene-environment interaction e.g. carriers of the variant allele extract more nicotine and toxins from each cigarette (Le Marchand, 2008)
Genetic Epidemiology Example

- VanderWeele (2012) investigated direct and indirect effects using the approaches I illustrated today.

- The study sample consisted of 1836 cases and 1452 controls is from a case control study (cf. Miller et al., 2002) assessing the molecular epidemiology of lung cancer, which began in 1992 at the Massachusetts General Hospital (MGH).

- Eligible cases included any person over the age of 18 years, with a diagnosis of primary lung cancer that was further confirmed by an MGH lung pathologist.

- The controls were recruited from among the friends or spouses of cancer patients or the friends or spouses of other surgery patients in the same hospital.

- Potential controls that carried a previous diagnosis of any cancer (other than non-melanoma skin cancer) were excluded from participation.
Genetic Epidemiology Example

Using data simulated based on the distribution and effects found in the case control study we will

- Employ traditional approaches for mediation analysis
- Employ and compare counterfactual approaches for mediation analysis
- We will examine what proportion of the effect is due (i) to just mediation, (ii) to just interaction, (iii) to both and (iv) to neither
- We will use the STATA macros `paramed` and `med4way` at this purpose.
Conclusions

- Standard approaches to mediation analysis are subject to the problems of (i) unmeasured mediator-outcome confounding and (ii) the assumption of no interactions

- Either problem can give rise to very paradoxical results

- The potential outcomes framework has
  - provided alternative definitions of direct and indirect effects
  - made clear and more precise the no-unmeasured-confounding assumptions required for a causal interpretation
  - clarified the role of mediation and interaction in explaining total effect

- A variety of regression methods for causal mediation have been developed

- It’s good practice to assess sensitivity to the violation of the unmeasured-confounding assumptions.


References


References


