

Mediation Analysis in the presence of Exposure-Mediator Interaction: Theory and Method for Causal Inference

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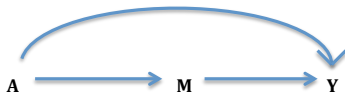
Mediation Analysis, the questions of interest

Let,

A be an exposure of interest,

M be an intermediate,

Y be an outcome.



Impact

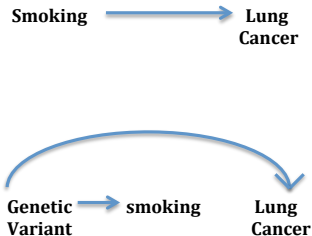
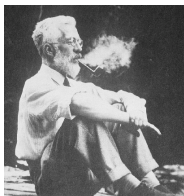
- Relevant across the Biomedical, Environmental and Social Sciences
- Etiology
- Prevention Science
- Policy Making

Agenda

1. Motivating Example: Variants on 15q25 associated with smoking and lung cancer
2. Traditional approaches to mediation analysis
3. Mediation analysis under the counterfactual framework for causal inference
4. Regression methods for mediation analysis in the presence of exposure-mediator interaction
5. Unification of Mediation and Interaction
6. Cancer epidemiology example: theory and method in practice (LAB)

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 Stefansson, 2010; Le Marchand, 2008)

Study Population (VanderWeele et al., 2012)

- 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

	Cases (N=1836)	Controls (N=1452)
Average Cigarettes per Day	25.42	13.97
Smoking Duration	38.50	18.93
Age	64.86	58.58
College Education	31.3%	33.5%
Male	50.1%	56.1%
rs8034191 C alleles		
0	33.8%	43.3%
1	48.5%	43.7%
2	17.7%	13.0%

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:

Cigarettes / day = 1.25 (0.00, 2.49) $P=0.05$

Again similar to other studies

Gene x Environment Interaction

Let Y denote lung cancer status, A denote the genetic variant, and M denote smoking status.

If we fit the logistic regression we get:

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

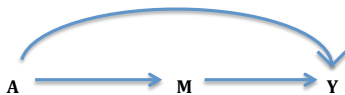
$$\theta_1 = 0.04, (-0.33, 0.41); \theta_2 = 1.33, (1.01, 1.64); \theta_3 = 0.49, (0.09, 0.89);$$

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 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:

$$\text{Indirect effect} = \phi_1 - \theta_1$$

$$\text{Direct effect} = \theta_1$$

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 $1\mu\text{g/g}$ 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 θ_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 :
 $\theta_2 \beta_1$

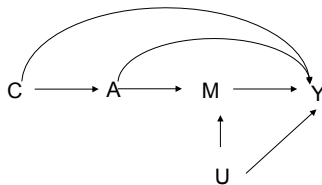
Traditional Approach to Mediation Analysis

- 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

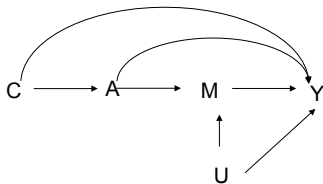


Mediator-Outcome Confounding

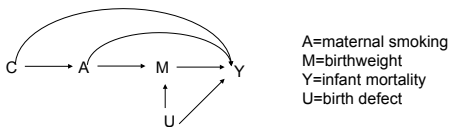
A number of studies (e.g. Yerushalmy, 1971; Wilcox, 1993; Hernandez-Diaz et al., 2006) have examined the effect of smoking A on infant mortality Y within strata of birthweight M

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!



Mediator-Outcome Confounding



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)

Exposure-Mediator Interaction

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 θ_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 θ_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:

$$\begin{aligned} Y_1 - Y_0 &= Y_{1M_1} - Y_{0M_0} \\ &= (Y_{1M_1} - Y_{1M_0}) + (Y_{1M_0} - Y_{0M_0}) \\ &= NIE + NDE \end{aligned}$$

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; Hanehan and Schwartz, 2009); they can be used for assessing mediation and for effect decomposition

Examples

Individual	M_0	M_1	Y_{00}	Y_{10}	Y_{01}	Y_{11}
1	0	1	0	1	0	1
2	1	1	0	1	0	0
3	0	1	0	0	0	1

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

$$TE = Y_1 - Y_0 = Y_{1M_1} - Y_{0M_0} = Y_{11} - Y_{00} = 1 - 0 = 1$$

$$CDE(m=0) = Y_{10} - Y_{00} = 1 - 0 = 1$$

$$CDE(m=1) = Y_{11} - Y_{01} = 1 - 0 = 1$$

$$NDE = Y_{1M_0} - Y_{0M_0} = Y_{10} - Y_{00} = 1 - 0 = 1$$

$$NIE = Y_{1M_1} - Y_{1M_0} = Y_{11} - Y_{10} = 1 - 1 = 0$$

Examples

Individual	M_0	M_1	Y_{00}	Y_{10}	Y_{01}	Y_{11}
1	0	1	0	1	0	1
2	1	1	0	1	0	0
3	0	1	0	0	0	1

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

$$TE = Y_1 - Y_0 = Y_{1M_1} - Y_{0M_0} = Y_{11} - Y_{01} = 0 - 0 = 0$$

$$CDE(m=0) = Y_{10} - Y_{00} = 1 - 0 = 1$$

$$CDE(m=1) = Y_{11} - Y_{01} = 0 - 0 = 0$$

$$NDE = Y_{1M_0} - Y_{0M_0} = Y_{11} - Y_{01} = 0 - 0 = 0$$

$$NIE = Y_{1M_1} - Y_{1M_0} = Y_{11} - Y_{11} = 0 - 0 = 0$$

Examples

Individual	M_0	M_1	Y_{00}	Y_{10}	Y_{01}	Y_{11}
1	0	1	0	1	0	1
2	1	1	0	1	0	0
3	0	1	0	0	0	1

For individual 3 (Total effect completely mediated, exposure-mediator interaction):

$$TE = Y_1 - Y_0 = Y_{1M_1} - Y_{0M_0} = Y_{11} - Y_{00} = 1 - 0 = 1$$

$$CDE(m=0) = Y_{10} - Y_{00} = 0 - 0 = 0$$

$$CDE(m=1) = Y_{11} - Y_{01} = 1 - 0 = 1$$

$$NDE = Y_{1M_0} - Y_{0M_0} = Y_{10} - Y_{00} = 0 - 0 = 0$$

$$NIE = Y_{1M_1} - Y_{1M_0} = Y_{11} - Y_{10} = 1 - 0 = 1$$

Question 1

Individual	M_0	M_1	Y_{00}	Y_{10}	Y_{01}	Y_{11}
1	0	1	0	1	0	1
2	1	1	0	1	0	0
3	0	1	0	0	0	1
4	1	0	1	1	0	1
5	0	1	0	1	1	1
6	0	1	0	0	1	1

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.

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 :

Individual	A	M_0	M_1	Y_{00}	Y_{10}	Y_{01}	Y_{11}
1	0	0	?	0	?	?	?
2	1	?	1	?	?	?	0
3	1	?	1	?	?	?	1

Mediation Analysis under Counterfactual Framework

We are able to estimate causal effects on average

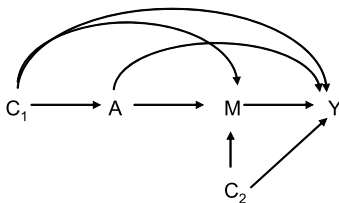
$$CDE(m) = E[Y_{1m} - Y_{0m}|C]$$

$$NDE = E[Y_{1M_0} - Y_{0M_0}|C]$$

$$NIE = E[Y_{1M_1} - Y_{1M_0}|C]$$

$$TE = NDE + NIE$$

(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??

Mediation Analysis under Counterfactual Framework

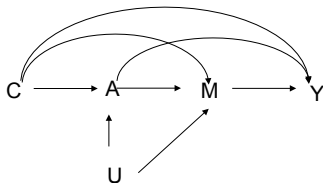
IDENTIFIABILITY ASSUMPTIONS:

- (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).

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?

Mediation Analysis under Counterfactual Framework

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

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)
- Macros for causal mediation analysis are available also in R (Imai et al., 2010; Steen et al, 2015)
- All these methods allow for exposure-mediator interactions

Continuous Outcome

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

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

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):

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

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

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

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

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

$$\begin{aligned} TE &= NDE + NIE \\ &= (\theta_1 + \theta_3\beta_0 + \theta_3\beta_1a^* + \theta_3\beta_2' C)(a - a^*) + (\theta_2\beta_1 + \theta_3\beta_1a)(a - a^*) \end{aligned}$$

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

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.

$$\begin{aligned}\text{logit}\{P(Y = 1|a, m, c)\} &= \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta'_4 c \\ E[M|a, c] &= \beta_0 + \beta_1 a + \beta'_2 c.\end{aligned}$$

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):

$$\begin{aligned}\log\{OR^{CDE}\} &= (\theta_1 + \theta_3 m)(a - a^*) \\ \log\{OR^{NDE}\} &\approx \{\theta_1 + \theta_3(\beta_0 + \beta_1 a^* + \beta'_2 c + \theta_2 \sigma^2)\}(a - a^*) + 0.5\theta_3^2 \sigma^2 (a^2 - a^{*2}) \\ \log\{OR^{NIE}\} &\approx (\theta_2 \beta_1 + \theta_3 \beta_1 a)(a - a^*)\end{aligned}$$

Binary Outcome

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

The outcome regression is logistic and thus consistently estimates the parameters that would be obtained in a cohort study (except the intercept which is not needed for the *NDE* or *NIE*):

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

The linear regression for the mediator cannot be applied directly to case-control data; instead if we have the prevalence π of the outcome we can obtain the estimates that we would have from a cohort study by weighting cases by π/p and controls by $(1 - \pi)/(1 - p)$ where p is the proportion of cases in the study (VanderWeele and Vansteelandt, 2010); We can run a weighted mediator regression:

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

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 $0.05 \times 1.2 = 0.06$ 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', we will discuss during lab)

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

SAS Macro for Mediation Analysis

The SAS macro takes this form:

```
%mediation(dat,yvar=,avar=,mvar=,cvar=,a0=,a1=,m=,yreg=,  
mreg=,interaction=)  
run;
```

- *dat* is the name of the dataset
- *yvar*, *avar*, *mvar* are the outcome, exposure and mediator
- *cvar* is the list of covariates [categorical must be recoded as binary]
- *a0* and *a1* are what we what have been calling a^* and a
- *m* is the value at which the controlled direct effects are evaluated
- *yreg* is specified as either *linear*, *loglinear*, *logistic*, *poisson*, *negbin*, *coxph*, *aft_exp*, *aft_weibull* [if outcome is failure time, censoring indicator needs to be specified]
- *mreg* is specified as either *linear* or *logistic*
- *interaction* is set to either TRUE or FALSE

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)

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 (INT_{ref}): The interaction if that operates only if the mediator is present in the absence of exposure
- (3) A mediated interaction (INT_{med}): 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

Component	Definition
Controlled Direct Effect (<i>CDE</i>)	$[Y_{10} - Y_{00}]$
Pure Natural Direct Effect (<i>PNIE</i>)	$[Y_{01} - Y_{00}][M_1 - M_0]$
Reference Interaction (<i>INT_{ref}</i>)	$[Y_{11} - Y_{10} - Y_{01} + Y_{00}]M_0$
Mediated Interaction (<i>INT_{med}</i>)	$[Y_{11} - Y_{10} - Y_{01} + Y_{00}][M_1 - M_0]$
$M_1 = 1[M_1 = m], M_0 = 1[M_0 = m]$	

- (1) CDE: Neither mediation nor interaction
- (1) INT_{ref}: Interaction but not mediation
- (1) INT_{med}: 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

Component	Average Causal Effects
$E[CDE]$	$p_{10} - p_{00}$
$E[INT_{ref}]$	$[p_{11} - p_{10} - p_{01} + p_{00}]P(M = 1 A = 0)$
$E[INT_{med}]$	$[p_{11} - p_{10} - p_{01} + p_{00}][P(M = 1 A = 1) - P(M = 1 A = 0)]$
$E[PNIE]$	$[p_{01} - p_{00}][P(M = 1 A = 1) - P(M = 1 A = 0)]$
$p_{10} = p_{a=1, m=0} = P(Y = 1 A = 1, M = 1)$	

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

$$\frac{E[CDE]}{E[TE]}, \frac{E[INT_{ref}]}{E[TE]}, \frac{E[INT_{med}]}{E[TE]}, \frac{E[PNIE]}{E[TE]}.$$

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 $E[PNIE]$ and $E[INTmed]$ for the overall proportion due to mediation:

$$\frac{E[PNIE] + E[INTmed]}{E[TE]}$$

Binary Outcome and Risk Ratio Scale

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:

$$\begin{aligned}RR_{a=1} - 1 &= k(RR_{10} - 1) \\&+ k(RR_{11} - RR_{10} - RR_{01} + 1)P(M = 1|A = 0) \\&+ k(RR_{11} - RR_{10} - RR_{01} + 1)\{P(M = 1|A = 1) \\&- P(M = 1|A = 0)\} \\&+ k(RR_{01} - 1)\{P(M = 1|A = 1) - P(M = 1|A = 0)\}\end{aligned}$$

where k is a scaling factor that is given by $k = \frac{p_{00}}{p_{a=0}}$.

Binary Outcome and Risk Ratio Scale

The proportion of the effect attributable to each of the 4 components is given by the expressions below:

$$PA_{CDE} = \frac{(RR_{10} - 1)}{(RR_{10} - 1) + (RERI)P(M = 1|A = 1) + (RR_{01} - 1)\{P(M = 1|A = 1) - P(M = 1|A = 0)\}}$$

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

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

$$PA_{PIE} = \frac{(RR_{01} - 1)\{P(M = 1|A = 1) - P(M = 1|A = 0)\}}{(RR_{10} - 1) + (RERI)P(M = 1|A = 1) + (RR_{01} - 1)\{P(M = 1|A = 1) - P(M = 1|A = 0)\}}$$

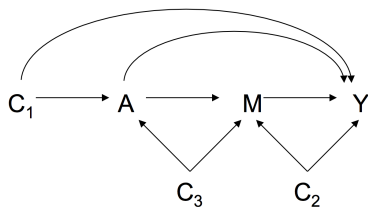
Unification of Mediation and Interaction

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:

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

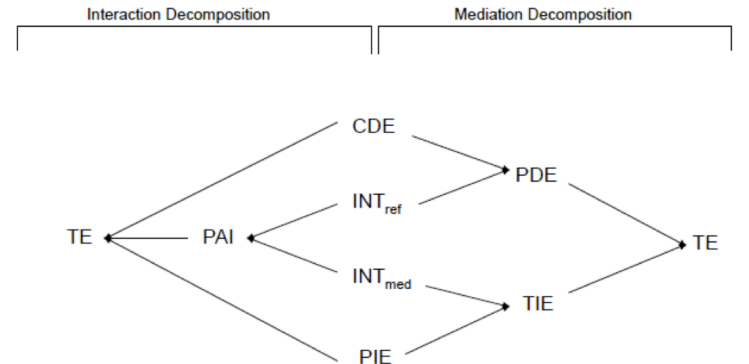
$$E[INT_{ref}] = \theta_3(\beta_0 + \beta_1 a^* + \beta_2' C)(a - a^*)$$

$$E[INT_{med}] = (\theta_3 \beta_1)(a - a^*)(a - a^*)$$

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

Relation to Decompositions

We can summarize the relations with prior decompositions in a figure:



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

Sensitivity Analyses

- Sensitivity analysis techniques have been developed to assess the impact of the violation of no-unmeasured confounding assumptions (VanderWeele, 2010; Imai et al, 2010)
- Sensitivity analysis techniques have been developed to assess the impact of selection bias (Valeri and Coull, 2016)
- Approaches for measurement error and misclassification correction have been developed (Valeri and VanderWeele, 2013; Valeri, Lin and VanderWeele, 2013; Valeri et al., 2016)
- A possible approach to sensitivity analysis to unmeasured confounding is to report how large the effects of the confounder should be to completely explain away the effect
- A similar approach to sensitivity analysis to measurement error is to report how large error should be to completely explain away the effect

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

- BARON, R.M. KENNY, D.A. (1986). The Moderator-Mediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical Considerations. *Journal of Personality and Social Psychology* 51: 1173-1182.
- IMAI, K., TINGLEY, D. and YAMAMOTO, T. (2010). A General Approach to Causal Mediation Analysis. *Psychological Methods*, Vol. 15:309-334.
- MACKINNON, D. P. (2008). *Introduction to Statistical Mediation Analysis*. New York: Erlbaum.
- MILLER, D.P., LIU, G., De VIVO, I., LYNCH, T.J., WAIN, J.C., SU, L. CHRISTIANI, D.C. Combinations of the variant genotypes of GSTP1, GSTM1, and p53 are associated with an increased lung cancer risk. *Cancer Res*, 62, 2819-23 (2002).
- PEARL, J. (2001). Direct and Indirect Effects. *Proceedings of the Seventeenth Conference on Uncertainty in Artificial Intelligence*, San Francisco, CA: Morgan Kaufmann, 411-420.
- ROBINS, J.M. & Greenland S. (1992). Identifiability and exchangeability for direct and indirect effects. *Epidemiology*, 3:143-155.
- VALERI, L., LIN, X., and VANDERWEELE, T.J. (2014) Mediation analysis when the mediator is measured with error and the outcome follows a generalized linear model. *Statistics in Medicine*
- VALERI, L., and VANDERWEELE, T.J. (2013). Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychological Methods*.
- VALERI, L. and VANDERWEELE, T.J.,(2014) The estimation of direct and indirect causal effects in the presence of a misclassified binary mediator. *Biostatistics*
- VANDERWEELE, T.J. (2010). Bias formulas for sensitivity analysis for direct and indirect effects. *Epidemiology*, 21:540-551.
- VANDERWEELE, T.J., VANSTEELENDT, S. (2009).Conceptual issues concerning mediation, interventions and composition. *Statistics and its Interface* 2 457-468.
- VANDERWEELE, T.J. et al. (2012) Genetic variants on 15q25.1, smoking and lung cancer: an assessment of mediation and interaction. *American Journal of Epidemiology*.
- VANDERWEELE, T.J. (2014). A unification of mediation and interaction: a 4-way decomposition. *Epidemiology (Cambridge, Mass.)*, 25(5), 749-761.

STATA Macro for Mediation Analysis

The Stata command "paramed" was developed with Stata version 12 (Valeri and Vanderweele, 2013; Emsley et al., 2014).

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

The main options:

- Mediator: continuous or binary (linear or logistic)
- Outcome: continuous, binary, or count (linear, logistic, loglinear, Poisson or Negative Binomial)
- Exposure-Mediator Interaction option
- Case control design option
- Non-rare outcome option (log-linear model)
- Output: marginal and conditional causal effects (as defined in Pearl, 2001 and Robins and Greenland, 1992) and proportion mediated

STATA Mediation Macro main options

The command can be used with the following statement:

```
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

mreg() the mediator regression model

STATA Macro additional options

paramed outcomevar, avar() mvar() cavar() a0() a1() m() yreg() mreg()

The option "nointer" exclude exposure-mediator interaction from 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. See next slide); 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 to specify seed

The option "level()" can be used to specify the level at which the confidence interval is calculated.