Causal Mechanisms Short Course Part IV

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Plan of Presentation

(1) Review of identification assumptions

(2) Direct and indirect effects on a ratio scale

(3) Analytic formulas versus Monte Carlo approach

(4) SAS (and SPSS) macros

(5) Comparison with standard approaches

(6) Pitfalls, caveats, and examples

Identification of Direct and Indirect Effects

To estimate natural direct and indirect effects (for a causal diagram interpreted as a set of non-parametric structural equations) we need:

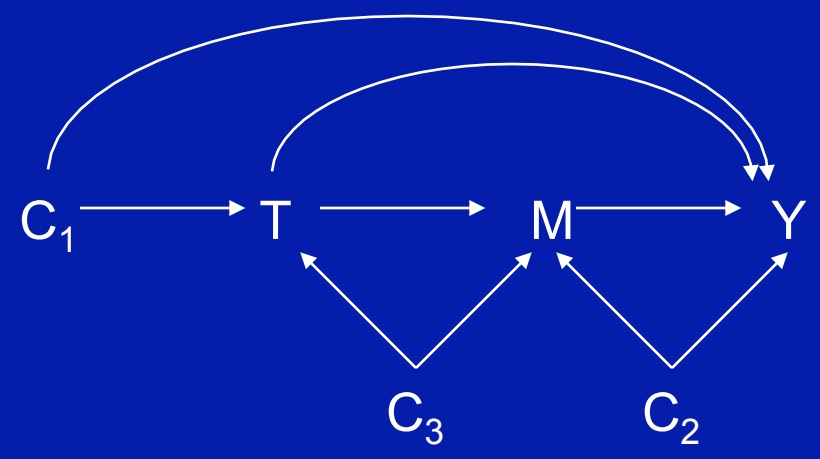
(1) There are no unmeasured treatment-outcome confounders given C

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

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

(4) The mediator-outcome confounders are not affected by treatment

Note (1) and (3) are guaranteed when treatment is randomized



Odds Ratios for Mediation Analysis

In many disciplines for a binary outcome, ratio scales are used (e.g. odds ratios and risk ratios)

One can similarly define effects on the odds ratio scale (VanderWeele and Vansteelandt, 2010)

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

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

We can give similar definitions for natural direct and indirect effect odds ratios

On the odds ratio scale we have: TE = NDE x NIE

Comparison of Software/Approaches

As compared with the R and Stata software, the SAS and SPSS software:

-Essentially uses the same assumptions

-Estimates the same types of effects

However…

-When the outcome is binary, the SAS/SPSS software uses a ratio scale rather than a difference scale (R/Stata)

-The SAS/SPSS software uses analytic formulas and the delta methods for estimation and standard errors (faster) rather than a Monte Carlo approach as in R/Stata (more general)

Regression for Causal Mediation Analysis

Suppose identification assumptions hold and we fit the following two regressions accommodating exposure-mediator interaction:

$E[Y|T=t,M=m,C=c] = \theta_0 + \theta_1 t + \theta_2 m + \theta_3 tm + \theta_4' c$

$E[M|T=t,C=c] = \beta_0 + \beta_1 t + \beta_2' c$

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

$CDE(m) = (\theta_1+\theta_3 m)$

$NDE = (\theta_1+\theta_3\beta_0+\theta_3\beta_2' c)$

$NIE = (\theta_2\beta_1+\theta_3\beta_1)$

Expressions are available for non-binary treatment as well

Regression for Causal Mediation Analysis

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

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

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

where σ^{θ}_{ij} is the covariance between estimates of θ_i and θ_j in the regression model for Y and σ^{β}_{ij} is the covariance between estimates of β_i and β_j in the regression model for M (VanderWeele and Vansteelandt, 2009)

The variance expression for the NDE is somewhat more complicated

SAS/SPSS macros will do this automatically

Odds Ratios for Mediation Analysis

With a binary outcome if we fit a logistic model for the outcome allowing for interaction:

$\text{logit}[P(Y=1|T=t,M=m,C=c)] = \theta_0 + \theta_1 t + \theta_2 m + \theta_3 tm + \theta_4' c$

$E[M|T=t,C=c] = \beta_0 + \beta_1 t + \beta_2' c$

Then provided that the <u>outcome is rare</u> (or using log linear models/RR's instead of a logistic model) we can combine the estimates to get the following formulas for direct and indirect effects (VanderWeele and Vansteelandt, 2010):

$\log\{CDE^{OR}(m|c)\} = (\theta_1+\theta_3 m)$

$\log\{NDE^{OR}(c)\} = (\theta_1+\theta_3(\beta_0+\beta_2' c+\theta_2\sigma^2)) + 0.5\theta_3^2\sigma^2$

$\log\{NIE^{OR}(c)\} = (\theta_2\beta_1+\theta_3\beta_1)$

where σ^2 is the error variance in the linear regression for M

Similar to the continuous Y formulas but with extra NDE terms involving σ^2

Odds Ratios for Mediation Analysis

Similar expressions are likewise available for binary mediators (Valeri and VanderWeele, 2012)

Similar expressions can also be obtained for count outcomes using either Poisson or Negative Binomial outcome regression models (Valeri and VanderWeele, 2012)

The SAS/SPSS macros can accommodate these cases

Eventually mediation for time-to-event outcomes (VanderWeele, 2011) will also be accommodated

Sensitivity analysis (somewhat different approach, VanderWeele, 2010) also to be implemented soon…

Macro for Mediation Regression

These mediation analyses can be run automatically using a SAS macro (Valeri and VanderWeele, 2012):

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

where:

dat is the name of the dataset

yvar, avar, mvar are the outcome, exposure/treatment and mediator

cvar is the list of covariates [categorical covariates must be recoded as binary indicator variables; SAS macro dumvar can be useful for this]

a0 and a1 are the treatment levels being compared (often 0 and 1 respectively)

m is the value at which the controlled direct effects are evaluated

nc is the number of covariates listed in cvar

yreg is specified as either linear, loglinear, logistic, poisson, or negbin

mreg is specified as either linear or logistic

interaction is set to either TRUE or FALSE

Macro for Mediation Regression

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

The default for output is “REDUCED”

If output is listed as “FULL” then this will also report “total direct effects” and “pure indirect effects”

If output is set to “FULL” then the macro will also calculate the various effects conditional on the value of c that is specificed by the “c=“ statement

Otherwise the macro will calculate the direct and indirect effects evaluated at the mean level of C in the data

If boot=TRUE is specified, standard errors are calculated using bootstrapping (default is 1000 samples) rather than using the delta method; this may be preferable if the sample size is small

If e.g. boot=5000 is specified the macro will use 5000 bootstrapped samples

If casecontrol=TRUE is specified, the macro will assume case-control data and fit the mediator regression model only for the controls and assume the outcome is rare

Macro for Mediation Regression

Here is an example when no covariates are included:

```
%mediation(dat,yvar=satis,avar=therapy,mvar=attrib,cvar= ,a0=0,a1=1,m=0.3,nc=,
yreg=linear ,mreg=linear,interaction=true)
run;
```

For looking at the extent to which the effects of a therapy program on life satisfaction are mediated through attitudes to negative life experience

The SAS output includes:

(1) The results of the outcome regression

(2) The results of the mediator regression

(3) Estimates of the controlled direct effect, natural direct effect and natural indirect effect

Macro for Mediation Regression

For example the output for the outcome regression for life satisfaction is as follows:

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	1	-0.19161	0.23164	-0.83	0.4157
therapy	1	0.43079	0.32898	1.31	0.2018
attrib	1	0.38333	0.25837	1.48	0.1499
int	1	0.04181	0.36848	0.11	0.9105

The output for the mediator regression for positive attribution is:

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	1	-0.35357	0.21837	-1.62	0.1166
therapy	1	0.81857	0.29902	2.74	0.0106

Macro for Mediation Regression

The final output for the direct and indirect effects is then:

Obs	Effect	Estimate	s_e_	p_value	_95__CI_ lower	_95__CI_ upper
1	cde	0.47260	0.47647	0.32126	-0.46128	1.40648
2	nde	0.41601	0.36234	0.25091	-0.29417	1.12619
3	nie	0.34801	0.24981	0.16360	-0.14163	0.83764
4	total effect	0.76402	0.31545	0.01543	0.14574	1.38229
5	proportion mediated	0.45550				

The SPSS macro works in essentially exactly the same manner

Details are available in Valeri and VanderWeele (2012)

For continuous outcomes these should give nearly identical results to the R/Stata program

For dichotomous outcomes one gets effects on the ratio scale using the SAS/SPSS macros but on the difference scale with R/Stata

Standard Approach

There are two standard approaches often employed for mediation:
(1) "Difference Method" (common in epidemiology)
(2) "Product Method" (common in social sciences)

Difference method regresses outcome on treatment:

$E[Y|T=t,C=c] = \phi_0 + \phi_1 t + \phi_2' c$

And compares the estimate ϕ_1 of treatment T with the estimate θ_1 obtained when including the potential mediator M in the regression model

$E[Y|T=t,M=m,C=c] = \theta_0 + \theta_1 t + \theta_2 m + \theta_4' c$

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

Indirect effect = $\phi_1 - \theta_1$
Direct effect = θ_1

Standard Approach

The other standard method, used more commonly in the social sciences is sometimes referred to as the "product method" (Baron and Kenny, 1986):

One regresses M on T: $E[M|T=t,C=c] = \beta_0 + \beta_1 t + \beta_2' c$

One regresses Y on M and T: $E[Y|T=t,M=m,C=c] = \theta_0 + \theta_1 t + \theta_2 m + \theta_4' c$

The direct effect is once again θ_1

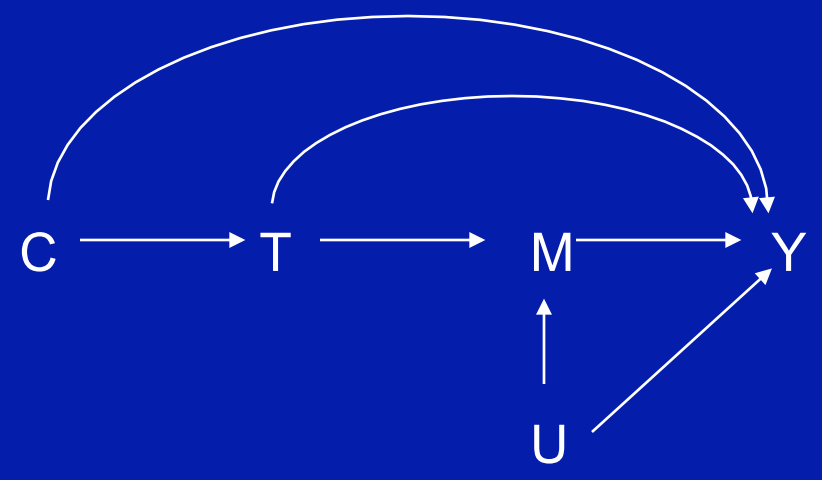
The indirect or mediated effect is the product of the coefficient of T in the regression for M times the coefficient of M in the regression for Y: $\beta_1\theta_2$

The product method and difference method will coincide for continuous outcomes provided but not for binary outcomes (MacKinnon and Dwyer, 1993, MacKinnon et al., 1995)

Standard Approach

The standard approaches to mediation analysis are subject to <u>two important limitations</u>

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



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

Standard Approach

PROBLEM 2: The standard approach presupposes presupposes no interactions between the effects of the treatment and the mediator on the outcome:

$E[Y|T=t,M=m,C=c] = \theta_0 + \theta_1 t + \theta_2 m + \theta_4' c$

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

$E[Y|T=t,M=m,C=c] = \theta_0 + \theta_1 t + \theta_2 m + \theta_3 tm + \theta_4' c$

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

If we fit the model without the interaction

$E[Y|T=t,M=m,C=c] = \theta_0 + \theta_1 t + \theta_2 m + \theta_4' c$

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

Standard Approach

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

$E[Y|T=t,M=m,C=c] = \theta_0 + \theta_1 t + \theta_2 m + \theta_4' c$

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 treatment T is close to 0

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

Furthermore, we might have an interaction between the effects of T and M on Y even if T 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!

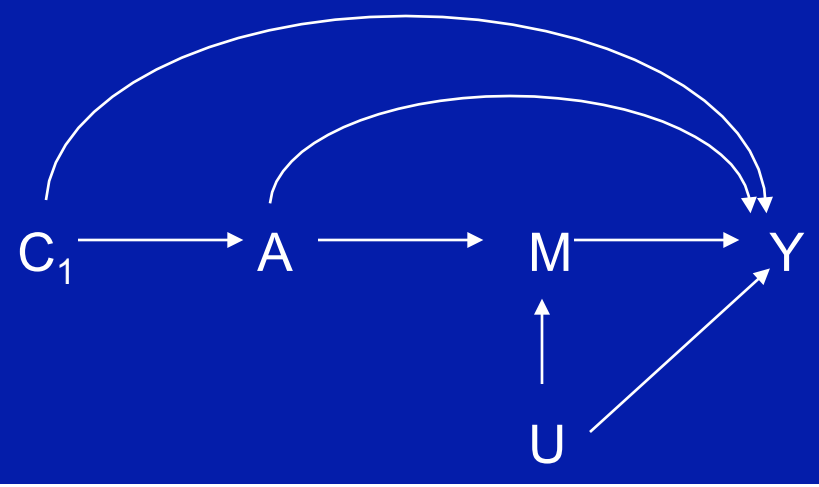
These problems are NOT simply hypothetical…

Mediator-Outcome Confounding

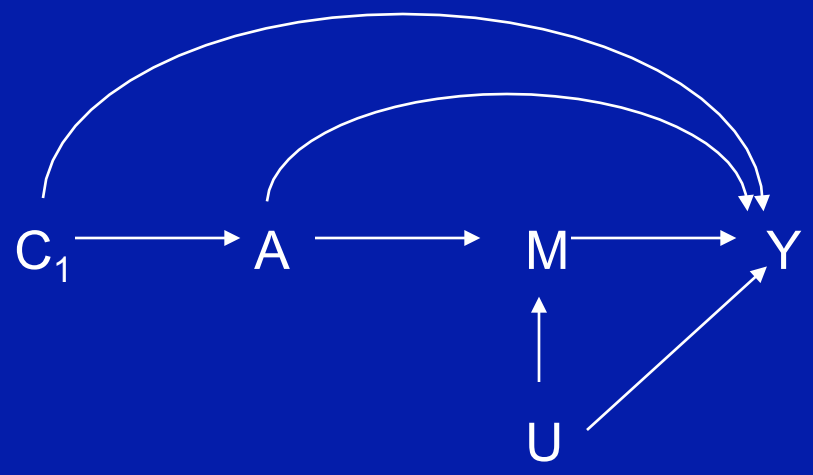
A number of studies (e.g. Yerushalmy, 1971; Wilcox, 1993; Hernandez-Diaz et al., 2006) have examined the effect of smoking A on infant mortality Y within strata of birthweight M

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

Studies have found that amongst those with the lowest birth weight, smoking appears to have a beneficial effect!!! e.g. 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



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

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

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

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

Treatment-Mediator Interactions

Mann et al. (2011) used 122,476 mother-infant pairs in the South Carolina Medicaid program between 1996 and 2002 to study associations between pre-eclampsia (T) and cerebral palsy (Y) by preterm birth status (M)

The odds ratio comparing pre-eclampsia vs. no pre-eclampsia are:

0.73 (95% CI: 0.42,1.26) for preterm infants
3.46 (95% CI: 1.42, 8.41) for term infants

Pre-eclampsia appears to have a protective effect for preterm infants

Probably this is due to a common cause of preterm birth and cerebral palsy for which control was not made (e.g. intrauterine infection)

Simple sensitivity analysis (cf. VanderWeele and Hernandez-Diaz, 2011) suggests a more plausible range for the “direct effect” for preterm infants is perhaps 1.04 to 1.59

There is a detrimental effect for both preterm and term infants

Treatment-Mediator Interactions

Both pitfalls seem to be present here; there is unmeasured confounding and also clearly interaction:

0.73 (95% CI: 0.42,1.26) for preterm infants
3.46 (95% CI: 1.42, 8.41) for term infants

The two problems might combine here in a rather bizarre way; the naïve analysis suggests a negative direct effect for preterm infants and positive direct effect for term infants; because these are in different directions, ignoring the interaction might give us something not too far from a null controlled direct effect

The standard conclusion would then be all the effect is mediated (once the mediator is in the model the effect of exposure is null)

This would be the opposite of our more reasoned conclusion of a strong direct effect; the two problems of interaction and no unmeasured confounding essentially would combine here to give precisely the wrong conclusion!

Standard Approach

The various approaches in causal inference help address some of these limitations:

(1) They point out the need to control for mediator-outcome confounding and give sensitivity analysis techniques for when there are important unmeasured mediator-outcome confounders

(2) They can accommodate treatment-mediator interactions, more complex models, non-linear models; they are based on a very general non-parametric approach

The standard approach is not always incorrect but careful thought needs to be given to the issues of (1) mediator-outcome confounding and (2) interaction/non-linearities before using it

Historical Conclusion

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

However a later paper in the psychology literature (Baron and Kenny, 1986) came to be the canonical reference for mediation analysis in the social sciences (>30,000 citations on Google Scholar)

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

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

Contrary to claims made in the psychology literature, mediator-outcome confounding is an issue even in randomized trials!

Summary

We have provided:

(1) Introduction to Potential Outcomes

(2) Concepts and assumptions from counterfactual-based approaches to mediation analysis

(3) Software to implement in R / Stata

(4) Software to implement in SAS / SPSS

(5) Reminder of key assumptions and pitfalls

We hope this was a helpful introduction to the material that will be presented in the conference

And we hope that you enjoy the conference…

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