

# Varieties of sensitivity analysis for mediation

Tyler J. VanderWeele  
Harvard School of Public Health  
Departments of Epidemiology and Biostatistics

# Plan of Presentation

- (1) Motivating Example: Variants on 15q25 associated with smoking and lung cancer
- (2) Unmeasured confounding and sensitivity analysis
- (3) Measurement error and sensitivity analysis
- (4) Genetics example revisited
- (5) How important is sensitivity analysis?

# 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)

However, 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

The study population of 1836 cases and 1452 controls is from a case control study of lung cancer at Massachusetts General Hospital (cf. Miller et al., 2002)

## Sample characteristics of cases and controls

		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%
Sex	Male	50.1%	56.1%
	Female	49.9%	43.9%
rs8034191 C alleles			
	0	33.8%	43.3%
	1	48.5%	43.7%
	2	17.7%	13.0%

# Associations of genetic variants with lung cancer

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

OR = 1.35 (1.21, 1.52)

P =  $3 \times 10^{-7}$

Similar to prior studies (Thorgeirsson et al., 2008; Hung et al., 2008; Amos et al., 2008)

# Associations of genetic variants with cigarettes per day

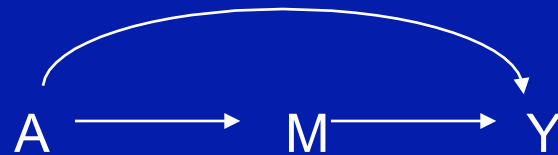
Associations between rs8034191 C alleles and cigarettes per day among smokers adjusting for smoking intensity, duration, age, sex and education gave:

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

Again similar to other studies

# Questions of Mediation

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



We could attempt to address this question using ideas of natural direct and indirect effects from the causal inference literature (Robins and Greenland, 1992; Pearl, 2001) and methods that allow for case-control study designs (VanderWeele and Vansteelandt, 2010)

# Definitions

Let  $Y$  denote some outcome of interest for each individual

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

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

Let  $C$  denote a set of covariates for each individual

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

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

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



# Definitions

Robins and Greenland (1992) and Pearl (2001) proposed the following counterfactual definitions for direct and indirect effects:

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

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

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

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

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

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

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

# Odds Ratios for Mediation Analysis

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  $M=m$

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

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:  $\text{TE} = \text{NDE} \times \text{NIE}$

# Identification of Direct and Indirect Effects

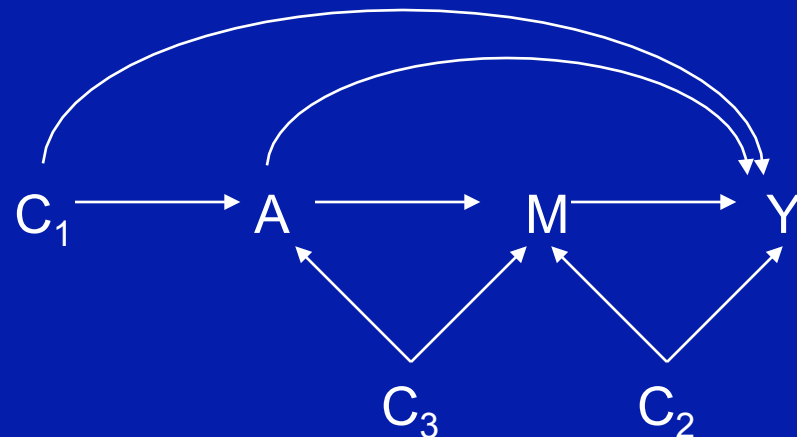
To estimate natural direct and indirect effects we need (on an NPSEM):

- (1) There are no unmeasured exposure-outcome confounders given C
- (2) There are no unmeasured mediator-outcome confounders given C
- (3) There are no unmeasured exposure-mediator confounders given C
- (4) The mediator-outcome confounders are not affected by exposure

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

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

Standard methods make similar assumptions



Formally, (1) is  $Y_{am} \perp\!\!\!\perp A \mid C$   
(3) is  $M_a \perp\!\!\!\perp A \mid C$

(2) is  $Y_{am} \perp\!\!\!\perp M \mid C, A$   
(4) is  $Y_{am} \perp\!\!\!\perp M_{a^*} \mid C$

# Mediator-Outcome Confounding

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

However a later paper in the psychology literature (Baron and Kenny, 1986) came to be the canonical reference for mediation analysis in the social sciences ( >35,000 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, though the point had been made five years earlier

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 sometimes made in the literature, mediator-outcome confounding is an issue even in randomized trials!

# Regression for Causal Mediation Analysis

We use regressions that accommodate exposure-mediator interaction:

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

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

Under assumptions (1)-(4), we can combine the estimates from the two models to get the following formulas for direct and indirect effects, comparing exposure levels  $a$  and  $a^*$  (VanderWeele and Vansteelandt, 2009):

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

$$NDE(a, a^*; a^*) = (\theta_1 + \theta_3(\beta_0 + \beta_1 a^* + \beta_2' E[C]))(a - a^*)$$

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

Standard errors can be obtained via the delta method or bootstrapping; SAS and SPSS macros can do this automatically (Valeri and VanderWeele, 2013) and have been translated into Stata (Emsley et al., 2013)

# Regression for Causal Mediation Analysis

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

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

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

which are the expressions often used for direct and indirect effects in the social science literature (Baron and Kenny, 1986) – the “product method”

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

The expressions with interaction are somewhat more complicated but can be obtained in a relatively straightforward way using standard regressions<sup>14</sup>

# Regression for Causal Mediation Analysis

Consider the use of the following two regression models, allowing for interaction between the genetic variant and smoking

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

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

Provided that the outcome is rare (or using log linear models/RR's instead of a logistic model) and identification assumptions (1)-(4) hold, we can combine the estimates to get the following formulas for direct and indirect effects (VanderWeele and Vansteelandt, 2010):

$$\log\{\text{CDE}(m)\} = (\theta_1 + \theta_3 m)(a - a^*)$$

$$\log\{\text{NDE}\} = (\theta_1 + \theta_3(\beta_0 + \beta_1 a^* + \beta_2 c + \theta_2 \sigma^2))(a - a^*) + 0.5\theta_3^2 \sigma^2 (a^2 - a^{*2})$$

$$\log\{\text{NIE}\} = (\theta_2 \beta_1 + \theta_3 \beta_1 a)(a - a^*)$$

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

The SAS/SPSS and Stata macros (Valeri and VanderWeele, 2013) can handle this; can also be used for dichotomous mediators and count outcomes

# Regression for Causal Mediation Analysis

The approach just described would be applicable to cohort data  
A modification is needed for case-control data (VanderWeele and Vansteelandt, 2010)

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):

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

The linear regression for the mediator cannot be applied directly to case-control data; instead if we have the prevalence  $\pi$  of the outcome

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

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 (e.g. 1836/3288)

Alternatively, one can use a 'controls only' analysis for the mediator



# Why might this approach fail?

## Confounding

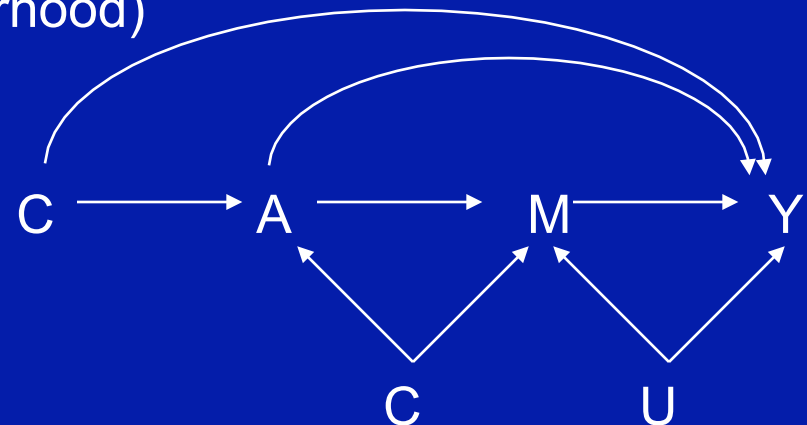
To use this approach with the genetic variants we need to assume no unmeasured confounding for the (1) exposure-outcome, (2) mediator-outcome, and (3) exposure-mediator relationships

Assumptions (1) and (3) are probably plausible for the exposure (the genetic variant) subject to no population stratification (the analysis was restricted to Caucasians)

\*(2)\* No confounding may be less plausible for the smoking – lung cancer association (e.g. SES / neighborhood)

We consider sensitivity analysis later

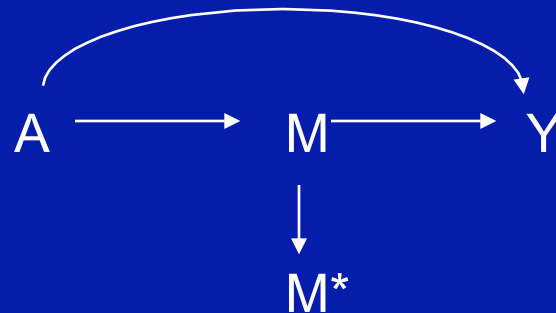
(4) Smoking duration may affect cigarettes/day and lung cancer and may be affected by the variant (though not much evidence) and results are similar when duration is omitted



# Why might this approach fail?

## Measurement Error

Cigarettes per day is self reported; it may be measured with error



If we use measured  $M^*$  rather than the true cigarettes per day  $M$  we may get bias...

Is this bias always in one direction? How can we assess it?

# Sensitivity Analysis and Confounding

## (1) Sensitivity analysis for controlled direct effects

- Risk Ratio / Odds Ratio Scale
- Additive Scale
- Hazard Difference or Hazard Ratio

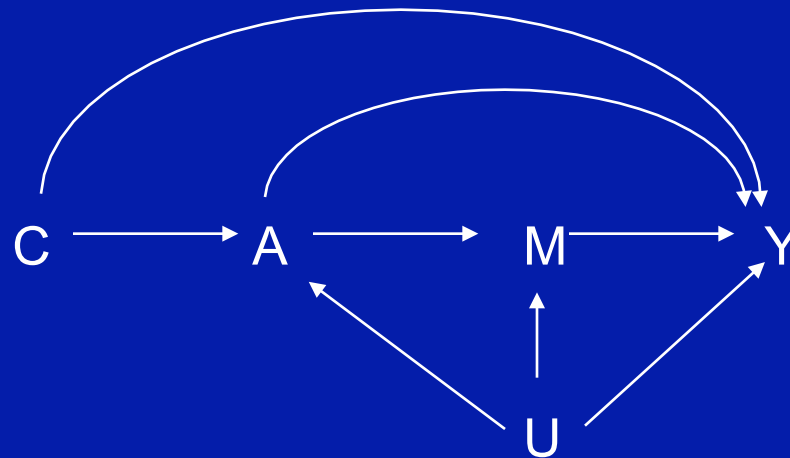
## (2) Sensitivity analysis for natural direct and indirect effects

- No exposure-mediator interaction
- Method involving the correlation of random errors
- Binary mediator, binary outcome

## (3) Sensitivity analysis for a mediator-outcome confounder affected by the exposure

# Sensitivity Analysis for CDEs

Suppose there is an unmeasured confounding of the mediator-outcome relationship (and/or exposure-outcome relationship)



So that controlling for (C,U) would suffice to control for confounding but not C alone i.e.  $Y_{am} \perp\!\!\!\perp A \mid (C,U)$  and  $Y_{am} \perp\!\!\!\perp M \mid C,A$

Our estimates of the controlled direct effect are biased if we have not adjusted for this variable U

# Sensitivity Analysis for CDEs

Suppose we wish to fit estimate the controlled direct effect on a risk ratio scale (approximated by odds ratios for a rare outcome). If we fit a logistic regression adjusted only for C:

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

The “direct” effect of the exposure A controlling for M will be  $\exp(\theta_1 + \theta_3 m)$

i.e.  $\text{CDE}^{\text{OR}}(m=0) = \exp(\theta_1)$

$$\text{CDE}^{\text{OR}}(m=1) = \exp(\theta_1 + \theta_3)$$

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

$$\text{Bias}(\text{CDE}_{a,a^*|c}^{\text{RR}}(m)) = \frac{P(Y|a, m, c)}{P(Y|a^*, m, c)} / \text{RR}_{a,a^*|c}^{\text{CDE}}(m)$$

# Sensitivity Analysis for CDEs

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

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

Then it can be shown (VanderWeele, 2010) that the bias factor is equal to:

$$B = \frac{1 + (\gamma - 1)\pi_{1m}}{1 + (\gamma - 1)\pi_{0m}}.$$

Where  $\pi_{1m}$  and  $\pi_{0m}$  are the prevalence U amongst with with (A=1,M=m) and (A=0,M=m) respectively

We could then specify different values of  $\gamma$ ,  $\pi_{1m}$  and  $\pi_{0m}$  and divide our estimates and confidence intervals by the bias factor “B” to assess what estimates we would have obtained had we been able to adjust for U

A similar approach can be used for settings in which the simplifying assumption of binary U with constant effect does not hold (VanderWeele<sub>22</sub> 2010) but the formulas are not quite as straightforward

# Sensitivity Analysis for CDEs

A similar approach also works for CDEs on the difference scale

Let Bias(CDE) 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)

$$B_{add}^{CDE}(m|c) = \{E[Y|a, m, c] - E[Y|a^*, m, c]\} - E[Y_{am} - Y_{a^*m}|c]$$

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 (VanderWeele, 2010): Suppose that no-confounding assumptions (1) and (2) hold for  $(C,U)$  where  $U$  is binary i.e.  $Y_{am} \perp\!\!\!\perp A \mid (C,U)$  and  $Y_{am} \perp\!\!\!\perp M \mid (C,U,A)$  then if the effect of  $U$  on  $Y$  is constant over  $a$ , and if we let

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

Then:

$$P(u|a, m, c) - P(u|a^*, m, c) = \delta$$

$$B_{add}^{CDE}(m|c) = \delta_m \gamma_m$$

We can use the bias formula by specifying:

- (i)  $\gamma$  = the risk ratio relating  $U$  and  $Y$ , conditional on  $A, M, C$
- (ii) the prevalence difference of  $U$  for the exposed vs. unexposed

Note these parameters may be different for different  $m$

Note that the prevalence difference is conditional on  $M=m$



# Sensitivity Analysis for CDEs

$$B_{add}^{CDE}(m|c) = \delta_m \gamma_m$$

Once we have calculated the bias term Bias(CDE) we can simply obtain our estimate of the CDE controlling only for C (e.g. fit a regression of Y on A,M,C) and we subtract Bias(CDE) 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

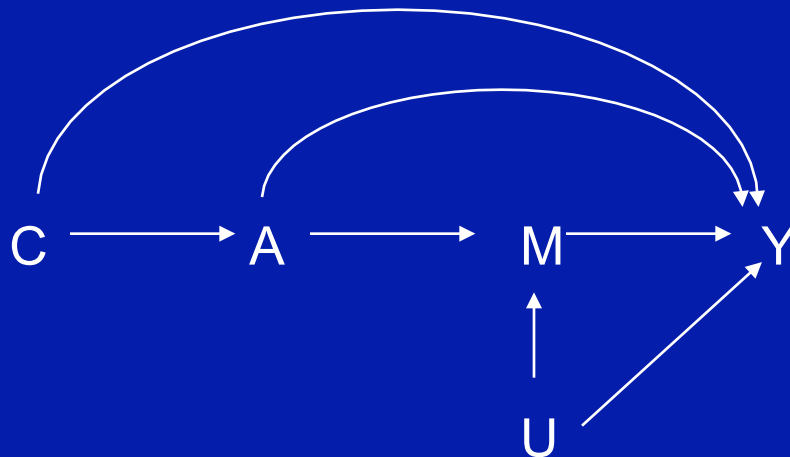
For conditional controlled direct effects, we can obtain corrected confidence intervals by subtracting Bias(CDE) from both limits of the confidence interval

Both 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, provided the outcome is rare, by replacing,  $\gamma$ , the risk ratio or outcome difference for the effect of U on Y by the hazard ratio or hazard difference for the effect of U on Y (VanderWeele, 2013)

# 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 (settings where U affects A, M and Y are still in progress)

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

There is still need for easier-to-use approaches

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

If there is no exposure-mediator interaction then NDE's equal CDE's

We could subtract our CDE bias formula  $B_{add}^{CDE}(m|c) = \delta_m \gamma_m$  from the NDE and its confidence interval

We could add this bias factor  $B_{add}^{CDE}(m|c) = \delta_m \gamma_m$  to the NIE and its CI

# Sensitivity Analysis for Natural Direct and Indirect Effects

2) Imai et al. (2010) give an approach for natural direct and indirect effects that is fairly easy to implement using an R program; it is possibly the most useful approach in the presence of interaction but 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

Suppose then for example, that the variables follow the regression models

$$Y = \phi_0 + \phi_1 A + \phi'_4 C + \epsilon_1$$

$$M = \beta_0 + \beta_1 A + \beta'_2 C + \epsilon_2$$

$$Y = \theta_0 + \theta_1 A + \theta_2 M + \theta_3 AM + \theta'_4 C + \epsilon_3$$

but that the errors terms  $\epsilon_2$  and  $\epsilon_3$  are correlated. Imai et al. (2010a) show that if one specifies the correlation between the errors terms in the second two regressions for  $M$  and  $Y$  as  $\rho$  then the natural indirect effect for example is given by:

$$NIE = \frac{\beta_1 \sigma_1}{\sigma_2} (\tilde{\rho} - \rho \sqrt{\{1 - \tilde{\rho}^2\} / (1 - \rho^2)})$$

where  $\sigma_1 = Var(\epsilon_1|A = 1)$ ,  $\sigma_2 = Var(\epsilon_2|A = 1)$ ,  $\tilde{\rho} = Cov(\epsilon_1, \epsilon_2|A = 1)$ , and  $\beta_1$  can all be estimated from the data. The parameter  $\rho$  could then be varied in a sensitivity analysis to examine how strongly the errors terms,  $\epsilon_2$  and  $\epsilon_3$ , in the regressions for  $M$  and for  $Y$ , would have to be

## Binary Outcome, Binary Mediator

3) We will consider one easier-to-use approach that can be applied when both the mediator and the outcome are binary

Suppose we had a binary outcome and binary mediator:

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

$$\text{logit}[P(M=1|A=a,C=c)] = \beta_0 + \beta_1 a + \beta_2' c$$

If controlling for C alone sufficed to control for confounding i.e. suffice to satisfy assumptions (1)-(4) then we would have (Valeri and VanderWeele, 2013):

$$OR_{a,a^*|c}^{CDE}(m) = \exp\{(\theta_1 + \theta_3 m)(a - a^*)\}$$

$$OR_{a,a^*|c}^{NDE}(a^*) = \frac{\exp(\theta_1 a) \{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta_2' c)\}}{\exp(\theta_1 a^*) \{1 + \exp(\theta_2 + \theta_3 a^* + \beta_0 + \beta_1 a^* + \beta_2' c)\}}$$

$$OR_{a,a^*|c}^{NIE}(a) = \frac{\{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2' c)\} \{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a + \beta_2' c)\}}{\{1 + \exp(\beta_0 + \beta_1 a + \beta_2' c)\} \{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta_2' c)\}}$$

## Binary Outcome, Binary Mediator

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  $Y$  for both strata of  $A$  and (ii) the prevalence of  $U$  in each exposure-mediator stratum,  $P(U|A=a, M=m, c)$  so that:

$$\begin{aligned}\gamma &= \frac{P(Y = 1|a, m, c, U = 1)}{P(Y = 1|a, m, c, U = 0)} \\ B_0 &= \frac{1 + (\gamma - 1)P(U = 1|a, M = 0, c)}{1 + (\gamma - 1)P(U = 1|a^*, M = 0, c)} \\ B_1 &= \frac{1 + (\gamma - 1)P(U = 1|a, M = 1, c)}{1 + (\gamma - 1)P(U = 1|a^*, M = 1, c)} \\ B_2 &= \frac{1 + (\gamma - 1)P(U = 1|a^*, M = 1, c)}{1 + (\gamma - 1)P(U = 1|a^*, M = 0, c)}\end{aligned}$$

From (i) and (ii) we can calculate  $B_0$ ,  $B_1$  and  $B_2$

## Binary Outcome, Binary Mediator

If we let

$$\begin{aligned}\theta_1^\dagger &= \theta_1 - \log(B_0) \\ \theta_2^\dagger &= \theta_2 - \log(B_2) \\ \theta_3^\dagger &= \theta_3 - \log(B_1) + \log(B_0).\end{aligned}$$

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

$$\begin{aligned}OR_{a,a^*|c}^{CDE}(m) &= \exp\{(\theta_1 + \theta_3 m)(a - a^*)\} \\ OR_{a,a^*|c}^{NDE}(a^*) &= \frac{\exp(\theta_1 a) \{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta'_2 c)\}}{\exp(\theta_1 a^*) \{1 + \exp(\theta_2 + \theta_3 a^* + \beta_0 + \beta_1 a^* + \beta'_2 c)\}} \\ OR_{a,a^*|c}^{NIE}(a) &= \frac{\{1 + \exp(\beta_0 + \beta_1 a^* + \beta'_2 c)\} \{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a + \beta'_2 c)\}}{\{1 + \exp(\beta_0 + \beta_1 a + \beta'_2 c)\} \{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta'_2 c)\}}\end{aligned}$$

This will give us the corrected natural direct and indirect had we been able to adjust for U as well

# Binary Outcome, Binary Mediator

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

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

$$\begin{aligned}\gamma &= \frac{P(Y = 1|a, m, c, U = 1)}{P(Y = 1|a, m, c, U = 0)} \\ B_0 &= \frac{1 + (\gamma - 1)P(U = 1|a, M = 0, c)}{1 + (\gamma - 1)P(U = 1|a^*, M = 0, c)} \\ B_1 &= \frac{1 + (\gamma - 1)P(U = 1|a, M = 1, c)}{1 + (\gamma - 1)P(U = 1|a^*, M = 1, c)} \\ B_2 &= \frac{1 + (\gamma - 1)P(U = 1|a^*, M = 1, c)}{1 + (\gamma - 1)P(U = 1|a^*, M = 0, c)}\end{aligned}$$

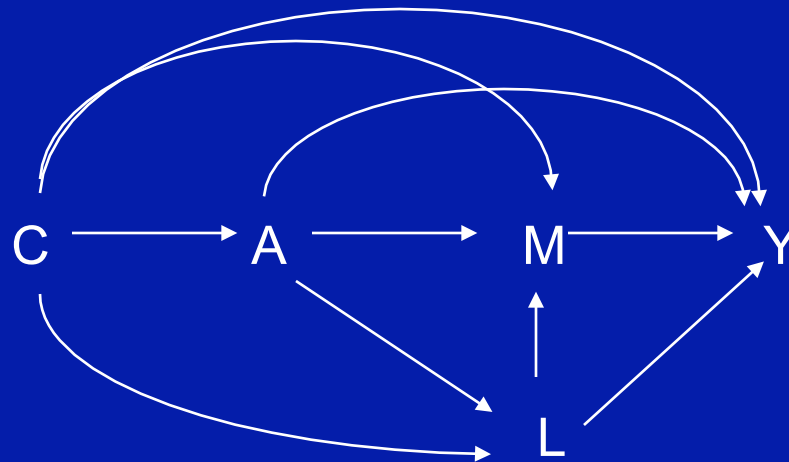
And then  $(\theta^\dagger_1, \theta^\dagger_2, \theta^\dagger_3)$  and the corrected effect estimates

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



# Mediator-Outcome Confounder Affected by Exposure

To estimate natural direct and indirect effects we need assumption 4 that there is no effect of exposure that confounds the mediator-outcome relationship; this would be violated in the following causal diagram:



One possibility may be to attempt to use sensitivity analysis techniques which would allow for inferring a range of possible values for the natural indirect effect under reasonable assumptions

# Mediator-Outcome Confounder Affected by Exposure

Current work consider sensitivity analysis when data is available on the exposure-induced mediator-outcome confounder  $L$  (e.g. Vansteelandt and VanderWeele, 2012; Imai and Yamamoto, 2013)

Other work considers sensitivity analysis when data is not available on the exposure-induced mediator-outcome confounder  $L$  (Tchetgen Tchetgen and Shpitser, 2012; VanderWeele and Chiba 2013)

Generally the latter are easier to implement in practice but the former are probably more reliable

If there is no “three-way interaction” (in different technical senses cf. Vansteelandt and VanderWeele, 2012; Imai and Yamamoto, 2013)<sub>3,4</sub> then the effects are identified with data on  $L$

# 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) Create a table with many values of all sensitivity analysis parameters; include those one thinks are too extreme; let the reader decide
- (2) Find the most important measured confounder variable; examine if an unmeasured confounder of similar strength would change conclusions
- (3) Report how large the effects of the confounder would have to be to completely explain away the effect
- (4) Use external data or expert opinion to inform sensitivity analysis parameters

# Measurement Error

Suppose  $M$  is measured with non-differential error:  $M^* = M + \varepsilon$

We fit the models:

$$\text{logit}[Y=1|A=a, M^*=m^*, C=c] = \theta_0 + \theta_1 a + \theta_2 m^* + \theta_3 a m^* + \theta_4' c$$

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

The model for  $M^*$  will give unbiased estimates for the model for coefficients for the model for  $M$

The coefficients in the model for  $Y$  will be biased when we use  $M^*$  instead of  $M$ ; we can obtain corrected estimates for the model for  $Y$  using methods of moments, regression calibration, or SIMEX (Valeri, Lin and VanderWeele, 2012) and corrected NIE and NDE estimates and s.e.'s once we specify:

$$\lambda = \text{Var}(M|A, C) / \text{Var}(M^*|A, C)$$

which we could vary in a sensitivity analysis

# Measurement Error

An especially easy case follows when there is no exposure mediator interaction:

$$\begin{aligned}\text{logit}[Y=1|A=a, M^*=m^*, C=c] &= \theta_0 + \theta_1 a + \theta_2 m^* + \theta_4' c \\ E[M^*|A=a, C=c] &= \beta_0 + \beta_1 a + \beta_2' c\end{aligned}$$

If we specify the proportion of the variance in  $M^*$  explained by  $M$ :

$$\lambda = \text{Var}(M|A, C) / \text{Var}(M^*|A, C)$$

we have that the true coefficients expressed in terms of the mismeasured (denote with the tilda “~”) are (Carroll et al., 2006; le Cessie et al., 2012):

$$\begin{aligned}\theta_1 &= \tilde{\theta}_1 - \tilde{\theta}_2 \left( \frac{1}{\lambda} - 1 \right) \beta_1 \\ \theta_2 &= \frac{\tilde{\theta}_2}{\lambda}.\end{aligned}$$

# Measurement Error

$$\begin{aligned}\theta_1 &= \tilde{\theta}_1 - \tilde{\theta}_2\left(\frac{1}{\lambda} - 1\right)\beta_1 \\ \theta_2 &= \frac{\tilde{\theta}_2}{\lambda}.\end{aligned}$$

We can then use our specification of  $\lambda$  and our estimates of the coefficient from the mismeasured mediator to get corrected coefficients and use those for our estimate of direct and indirect effects (le Cessie et al., 2012; VanderWeele et al., 2012)

We could vary  $\lambda$  in a sensitivity analysis

This approach also works with a continuous outcome

Standard errors can be estimated by bootstrapping

# Measurement Error

Methods have also been developed for other more complex forms of measurement error including:

- (1) Cases with exposure-mediator interaction (Valeri, Lin, and VanderWeele, 2012)
- (2) Binary mediators (Valeri and VanderWeele, 2012)
- (3) Differential measurement error with the exposure or outcome affecting the mediator measurement, differential or non-differential intra individual variation over time, and various trigger mechanisms (le Cessie et al., 2012)

Some of these techniques are more difficult to implement or require more specialized software

# Measurement Error

Intuitively we would expect the NIE to be biased towards the null and the NDE to be biased away from the null

When will this hold?

Assume NIE and NDE are in the same directions

Assume we have non-differential measurement error for M

We will have the intuitive conclusion (NIE toward null, NDE away) if:

- (1) M is binary (Ogburn and VanderWeele, 2012)
- (2) M is normally distributed and continuous but there is no interaction between M and A in either a linear or logistic model (VanderWeele et al., 2012)

Otherwise (e.g. if M has three or more levels; or M normal but there is AxM interaction) these intuitive results may not hold

However, we can still use sensitivity analysis (Valeri et al., 2012)



# Mediation Analysis for Genetic Variants on 15q25.1

If we apply the methods to the genetics data, tests for interaction b/w genetic variants and smoking is significant for rs8034191 ( $P=0.001$ )

Suppose we fit our models (ignoring unmeasured confounding and measurement error)

Allowing for gene x smoking interaction gives the following:

An increase of one rs8034191 C allele gives:

NDE OR = 1.32 (95% CI: 1.17, 1.49)  $P=9 \times 10^{-6}$

NIE OR = 1.01 (95% CI: 0.99, 1.03)  $P=0.16$

with proportion mediated 5.4%

It looks like most of the effect is through other pathways (i.e. not through cigarettes per day)

# Mediation Analysis for Genetic Variants on 15q25.1

We would expect unmeasured confounding here to be 'positive' (e.g. neighborhood would likely affect smoking and lung cancer in the same direction)

If so, NDE is biased downwards; NIE biased downwards  
This would strengthen the conclusion that most is direct (through other pathways)  
Our naïve NIE (already small) is an overestimate

What about measurement error?

Measurement error in cigarettes per day we might expect to bias the NIE downwards; the true NIE may be larger

This would threaten our conclusion

# Mediation Analysis for Genetic Variants on 15q25.1

We adjust the coefficients estimated in the outcome regression:

$$\text{logit}[Y=1|A=a, M^*=m^*, C=c] = \theta_0 + \theta_1 a + \theta_2 m^* + \theta_3 a m^* + \theta_4' c$$

for possible measurement error using regression calibration. The adjusted estimates can then be used to re-estimate direct and indirect effects.

Allowing up to 50% error gives (one allele rs8034191 C increase)

NDE OR = 1.27

NIE OR = 1.02

PM = 8.8%

Allowing up to 75% error gives (one allele rs8034191 C increase)

NDE OR = 1.33

NIE OR = 1.04

PM = 15.2%

Methods of moments, regression calibration, and SIMEX gave very similar results for measurement error correction

# Mediation Analysis for Genetic Variants on 15q25.1

There may be an indirect effect but it is quite small, even allowing substantial 75% measurement error (1.04 95% CI: 0.99,1.11)

Most of the effect seems through pathways other than cigarettes per day

Results were further replicated in 3 other lung cancer case-control studies (MD Andersen, IARC, Toronto) and gave similar conclusions

Results are quite robust to unmeasured confounding and measurement error

The effect of the variants on lung cancer is NOT through cigarettes per day

BUT... there is substantial interaction (likely no effect of the variants except in the presence of smoking; Li et al., 2010)

The variant may make each cigarette more harmful (more nicotine and toxins per cigarette smoked; Le Marchand et al., 2008) but do not operate on lung cancer principally by increasing cigarettes per day

May operate by deeper inhalation when smoking (current study at Bristol)

# How bad can it can get?

We have seen several sensitivity analysis techniques for unmeasured confounding and measurement error

However in our example from genetic epidemiology, our results seemed fairly robust to unmeasured confounding and to measurement error

We might wonder whether this will generally be the case

How important is sensitivity analysis?

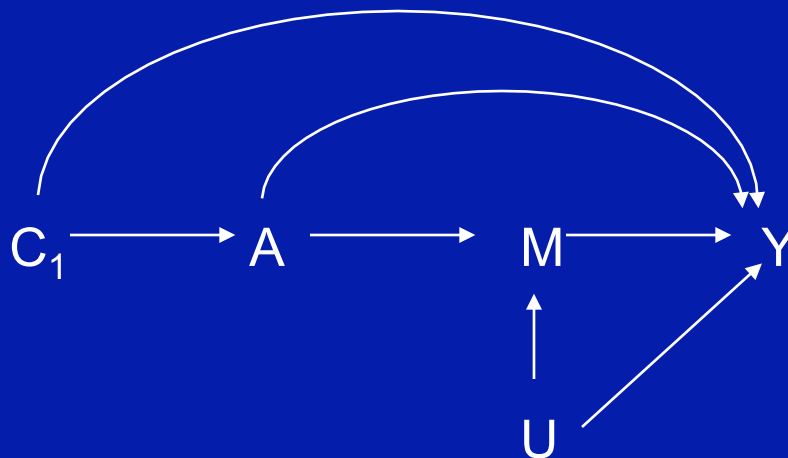
How biased can our results really be?

# Mediator-Outcome Confounding

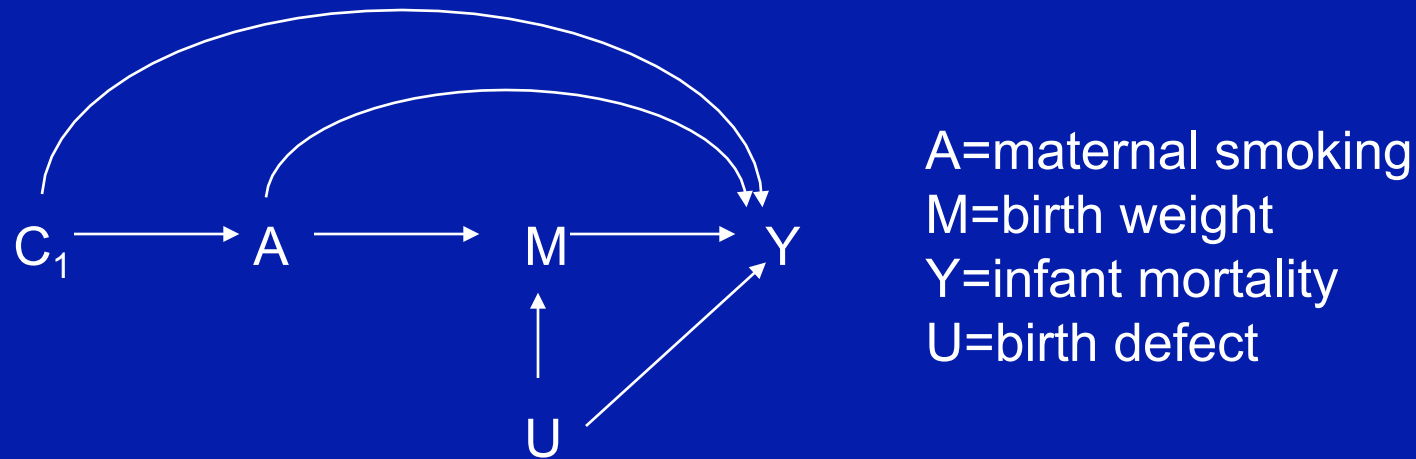
A number of studies (e.g. Yerushalmy, 1971; Wilcox, 1993; Hernandez-Diaz et al., 2006) have examined the effect of smoking A on infant mortality Y within strata of birthweight M

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



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<sub>47</sub>) we likely would not observe these paradoxical findings)

# Birthweight Paradox

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

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

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

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) then

$$\text{Bias(CDE)} = \{1 + (3.5 - 1) \times 0.025\} / \{1 + (3.5 - 1) \times (0.14)\} = 0.79$$

And our corrected estimate would be  $0.79 / \text{Bias(CDE)} = 0.79 / 0.79 = 1$   
and such confounding would completely explain away the birthweight paradox



# CBT Intervention

SMaRT trial (Strong et al., 2008): a randomized cognitive behavioral therapy intervention

Effect on depression symptoms after 3 months (SCL-20 depression)

At 3 months was  $E[Y|A=1]-E[Y|A=0]=-0.34$  (95% CI: -0.55, -0.13)

Intervention also had an effect on the use of antidepressant

Those in the CBT arm were more likely to use antidepressants

Does the CBT intervention affect depressive symptoms simply because of higher antidepressant use, or other pathways?

What happens when we regress outcome  $Y$  on treatment and mediator (anti-depressant use)...?

# CBT Intervention

The coefficient for antidepressant use is positive!

## It looks like antidepressant use increases depression!

The mediated effect through antidepressant use looks detrimental!

The “direct effect” looks larger than the total effect!

## What is going on here...? Mediator-Outcome Confounding

Those in more difficult situations both use an antidepressant and have higher levels of depressive symptoms

When we ignore this confounding we get paradoxical results!

Using a new sensitivity analysis techniques (Emsley and VanderWeele, 2013), data from several trials which randomize antidepressant use are used to inform sensitivity analysis parameters:

Direct effect ranges from: -.15 to -.28

Mediated effect (through antidepressant): -.06 to -.19

# Conclusions

- (1) New methodology for mediation analysis can help answer questions of pathways, but may be biased by confounding and measurement error
- (2) Sensitivity analysis methods for confounding and measurement error can help assess the extent to which these biases may invalidate results
- (3) A number of methods are now available but considerable work remains to be done in this area
- (4) The application of these methods suggests most of the effect of the variants on 15q25 on lung cancer is not through increasing cigarettes per day; similar approaches could be used with other SNPs, exposures and outcomes
- (5) Unmeasured confounding can lead to very biased estimates and paradoxical results and needs to be taken serious; sensitivity analysis can assist with this

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