Mediation analysis

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A short course on concepts and methods in Causal Inference

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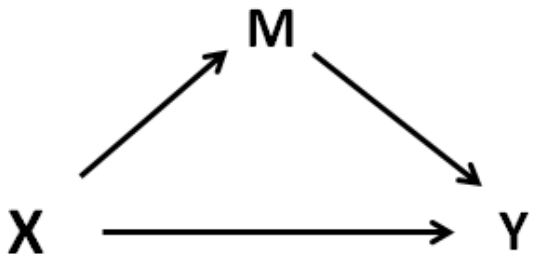
Introduction

Mediation analysis aims to disentangle the different pathways that could explain the effect of an exposure on the outcome

- molecular epidemiology
  - How much of the effect of chromosome 15q25.1 rs8034191 C allels on lung cancer is mediated by cigarettes smoked per day?
- social epidemiology
  - How much of the effect of SES in childhood on adult disease is mediated by SES in adulthood?
- life-course epidemiology
  - How much of maternal smoking on infant mortality is mediated by low birth weight?

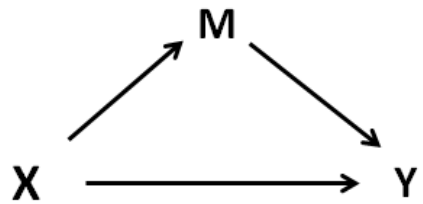
Framework



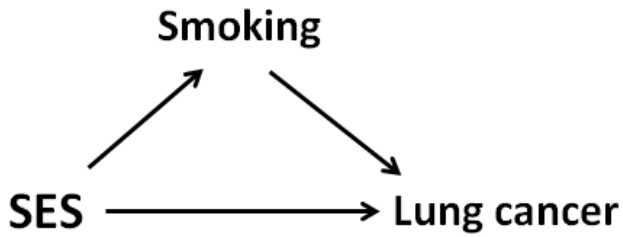
The aim is to assess the extent to which the total effect of the exposure is explained, or not explained, by a given set of hypothesized mediators

- $X \rightarrow M \rightarrow Y$: **indirect effect of X on Y**
- $X \rightarrow Y$: **direct effect of X on Y**

Traditional approach

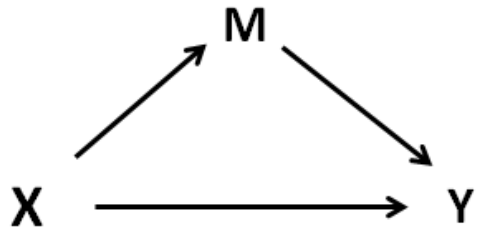


- consists of estimating the effect of X on Y for a given level of M (e.g. M=0) and of interpreting it as the direct effect of X on Y



- consists of estimating the effect of SES on lung cancer in non smokers and of interpreting it as the direct effect of SES on lung cancer, i.e. the effect not explained by smoking

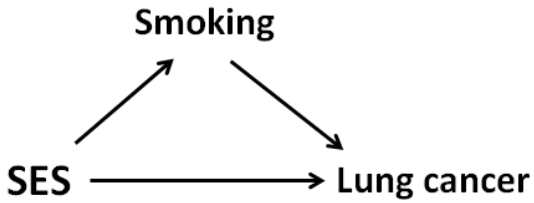
Traditional approach



- consists of fitting a regression model with Y as the outcome and X as the explanatory variable (total effect)
- consists of adding the covariate M into the model (direct effect)
- if the coefficient of X changes from the unadjusted (U) to the adjusted (A) model for M, there is evidence of mediation

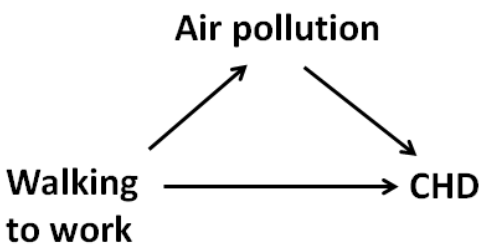
- Proportion of total effect explained by the mediator: RRu/RRa
- Percent excess risk explained by the mediator: $\frac{RRu-RRa}{RRu-1} * 100$

Example



- Crude relative risk of low vs high SES on lung cancer is equal to 2.3 (total effect)
- After adjustment for smoking the relative risk decreases to 1.2 (direct effect(?))
- Proportion of total effect explained by the mediator: $2.3/1.2 = 1.9$
- Percent excess risk explained by the mediator: $\frac{2.3-1.2}{2.3-1} * 100 = 85\%$

Note that the concept of proportion of the effect explained by the mediator can be unreliable in some situations: it is theoretically possible to have no total effect in presence of opposite direct and indirect effects

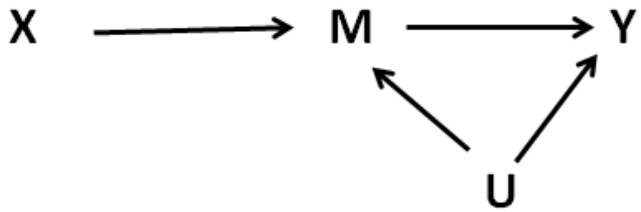


Issues

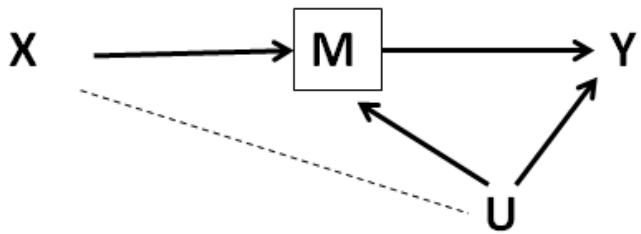
Traditional approaches to mediation analysis could give flawed conclusions in presence of:

- unmeasured/unknown mediator-outcome confounding
- exposure-mediator interaction
- mediator-outcome confounding affected by the exposure

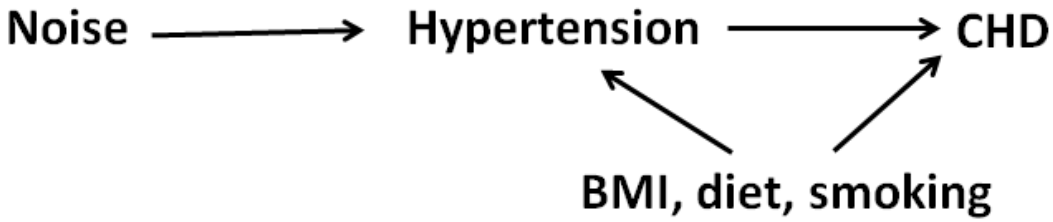
Mediator-outcome confounding



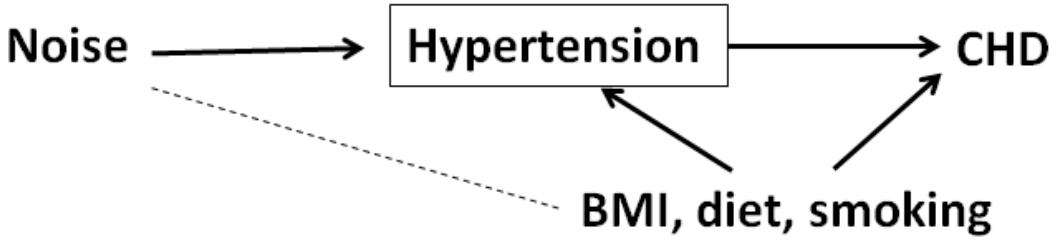
Conditioning on the mediator M induces a spurious association between X and U $\Rightarrow$ U becomes a confounder of the exposure-outcome association and induces bias (collider bias)



Example



Adjustment for hypertension introduces collider bias



All variables which affects both hypertension and CHD should be measured and controlled for in the analysis to estimate correctly the direct effect of noise on CHD

Sensitivity analysis for direct effect

- Could unmeasured/unknown mediator-outcome confounders explain away the estimated direct effect?
- Several authors addressed the issue of quantifying the bias introduced by conditioning on a collider: Bakely 2002; Greenland 2003; Pizzi 2011; Hafeman 2011; etc.
- Vanderweele (2010) proposed simplified formulas under specific assumptions (on the risk ratio scale):

$$B_m = \frac{1 + (\gamma_m - 1)\pi_{x,m}}{1 + (\gamma_m - 1)\pi_{x^*,m}}$$

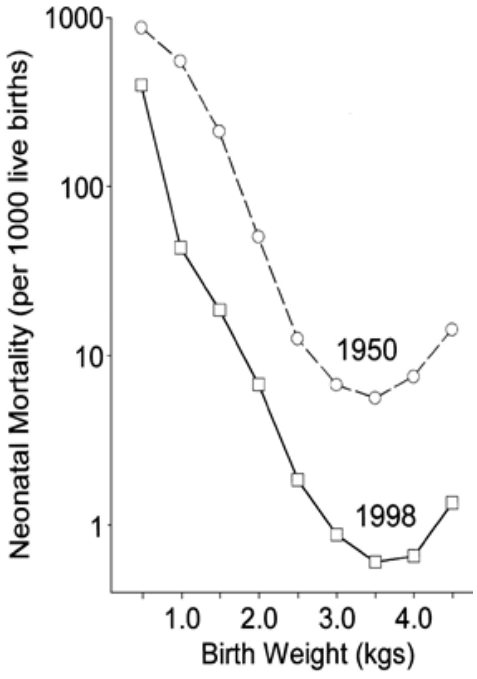
γ_m: direct effect of the unmeasured binary confounder U on the outcome for individuals with mediator level m

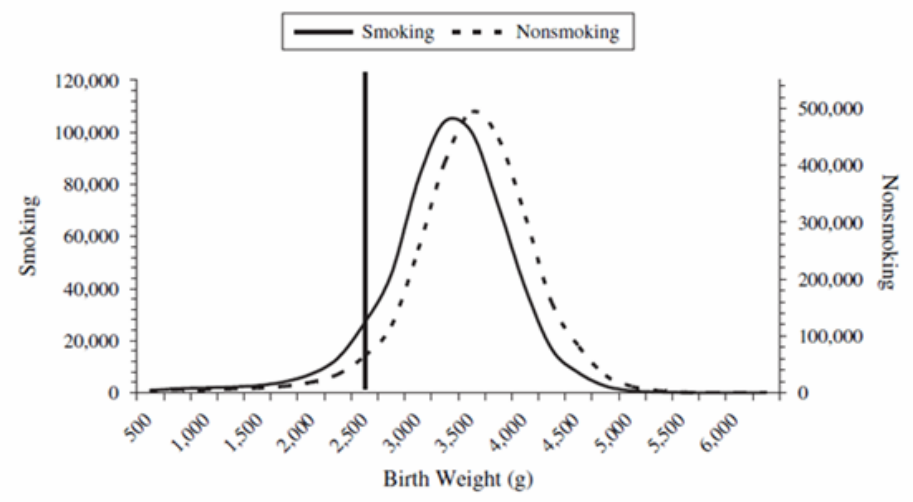
$\pi_{x,m}, \pi_{x^*,m}$: prevalence of the unmeasured confounder U among the two exposure levels x and x^* at a given level of the mediator m

- The ratio between the estimate not controlling for U and the estimate would have been obtained after controlling for U with the mediator set to level m is given by B_m

Birth weight and infant death

- Birth weight is a predictor of infant mortality
- Maternal smoking is a determinant of low birth weight



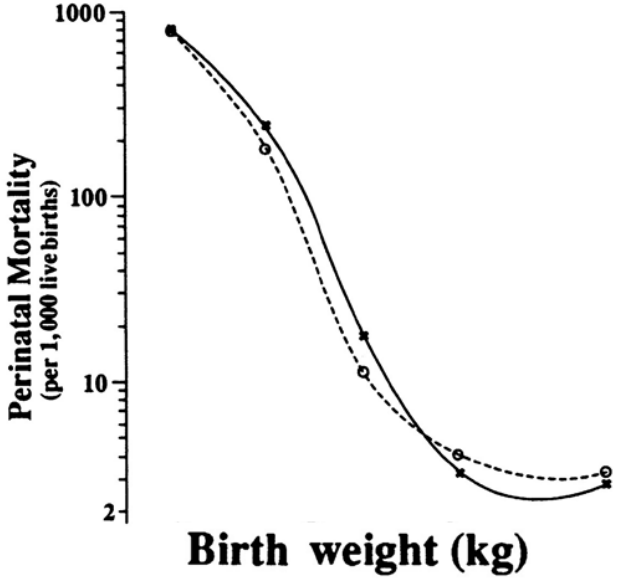


Wilcox A J Int. J. Epidemiol. 2001;30:1233-1241

Hernandez-Diaz S et al, Am J Epidemiol 2006

Low birth weight paradox

Crossover of birth weight specific mortality: smoking seems to be beneficial among low birth weight babies on infant mortality



Frequency distribution of birthweight and weight-specific perinatal mortality for infants exposed and unexposed to mothers' smoking: Missouri, 1980-1984

Wilcox A J Int. J. Epidemiol. 2001;30:1233-1241. Rerint of Wilcox A Am J Epidemiol 1993

Low birth weight paradox

3.000.000 infants born in US in 1991
Infant (1-year) mortality rate among

- Smokers: 1235 per 100.000
- Non smokers: 805 per 100.000
- Rate ratio: 1.53
- After adjustment for birth weight, rate ratio: 1.09

Stratification on birth weight

- Low birth weight: Rate ratio for smoking: 0.79
- Normal birth weight: Rate ratio for smoking: 1.80

Hernandez-Diaz S et al Am J Epidemiol 2006

Collider bias

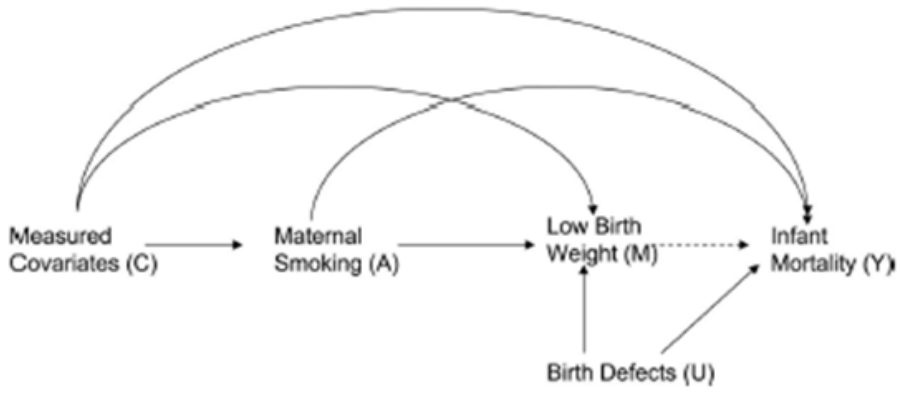


FIGURE. Diagram illustrating relationships between an exposure, eg, smoking (*A*); an intermediate, eg, low birth weight (*M*); an outcome, eg, infant mortality (*Y*); and both measured (*C*) and unmeasured (*U*) confounders.

A comparison of smoking with non smoking mothers, without controlling for birth defects, will artificially bias the comparison because in LBW infants, not smoking and LBW together is likely indicative of the presence of a birth defect.

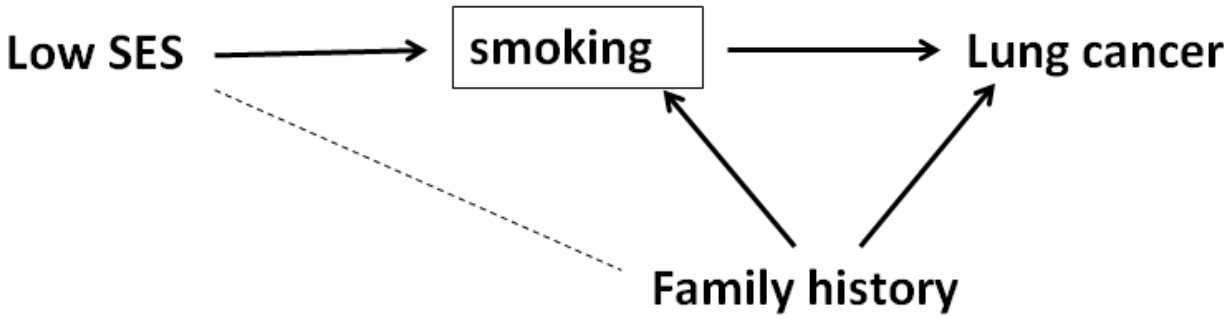
Sensitivity analysis

- Could collider bias explain away the estimated direct effect in LBW infants (RR=0.79)?
- Suppose:
  γ_m=3.5 (direct effect of birth defects on infant mortality)
  $\pi_{x,m}$=0.025 (prevalence of birth defects among low birth weigths infants with maternal smoking)
  $\pi_{x^*,m}$=0.14 (prevalence of birth defects among low birth weigths infants with no maternal smoking)

$$B = \frac{1 + (3.5 - 1) * 0.025}{1 + (3.5 - 1) * 0.14} = 0.79$$

- Correct-estimated direct effect: $0.79/0.79 = 1.00$
- if $\gamma = 5.0 \rightarrow B = 0.59 \rightarrow 0.79/0.59 = 1.34$

Example



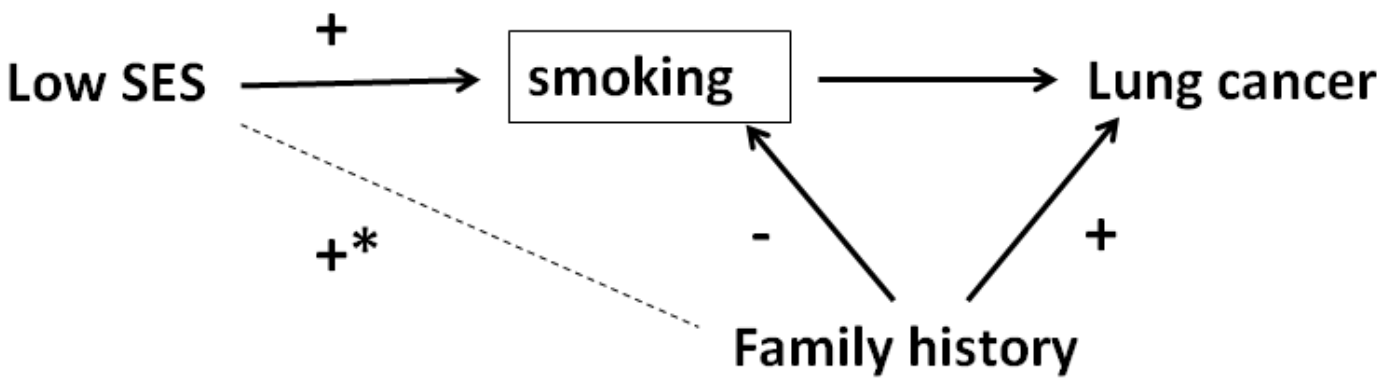
- Crude RR=2.3, adjusted RR=1.2
- Suppose:
  γ_m=2.5 (direct effect of positive family history on lung cancer)
  $\pi_{x,m}$=20% (prevalence of positive family history among non smokers/smokers and low SES men)
  $\pi_{x^*,m}$=5% (prevalence of positive family history among non smokers/smokers and high SES men)

$$B = \frac{1 + (2.5 - 1) * 0.20}{1 + (2.5 - 1) * 0.05} = 1.21$$

$$1.20/1.21 = 1.00$$

Sensitivity analysis

- Conditioning on a collider which is affected by two other variables (parents) induces a negative association between the parents if they affect the collider in the same direction, whereas the association is positive if the two parents affect the collider in opposite directions
- If there are interactions or non-linear association involved this rule may not apply (*)



- The bias is upwards, corresponding to an apparent harmful effect of low SES on lung cancer among non smokers/smokers

Exposure-mediator interaction

X	M	Risk	Cases	Non-cases	Total
0	0	1%	100	9900	10000
1	0	3%	150	4850	5000
0	1	2%	10	490	500
1	1	20%	200	800	1000

Total risk difference: 4.8%
Risk difference adjusted for M: 2.3%
Risk difference among those with M=0: DE(M=0)=2%
Risk difference among those with M=1: DE(M=1)=18%

$$(R_{X=1,M=1} - R_{X=0,M=0}) \neq (R_{X=1,M=0} - R_{X=0,M=0}) + (R_{X=0,M=1} - R_{X=0,M=0})$$

$$19\% \neq 2\% + 1\%$$

Exposure-mediator interaction

- The estimate of direct effect vary across different levels of the mediator $\Rightarrow$ presence of exposure-mediator interaction
- The total effect (TE) is the same, irrespectively of the mediator
- How to define the direct effect, i.e. the effect of the exposure on the outcome unexplained by the mediator?
- How to decompose the total effect into direct and indirect effects?

Counterfactual framework

- Counterfactuals are used to provide an alternative formal definition of direct effect as a population summary of the effects at different levels of the mediator
- In mediation analysis Y_{xm} is the potential outcome under the exposure level X=x and M=m (the hypothetical outcome that would be observed in the same individual at the same time under the exposure X=x and the mediator M=m)
- Controlled direct effects, natural direct effects and natural indirect effects

Total causal effect

Total causal effect: $Y_{xM_x} - Y_{x^*M_{x^*}} = Y_x - Y_{x^*}$

- *Contrast between the counterfactual outcome if the individual were exposed to $X = x$ and the counterfactual outcome if the same individual were exposed to $X = x^*$ with the mediator assuming whatever value it would have taken at the value of the exposure $X = x$ and $X = x^*$ respectively*

- Intuitively this effect captures the effect of X on Y via pathways that involve and not involve M

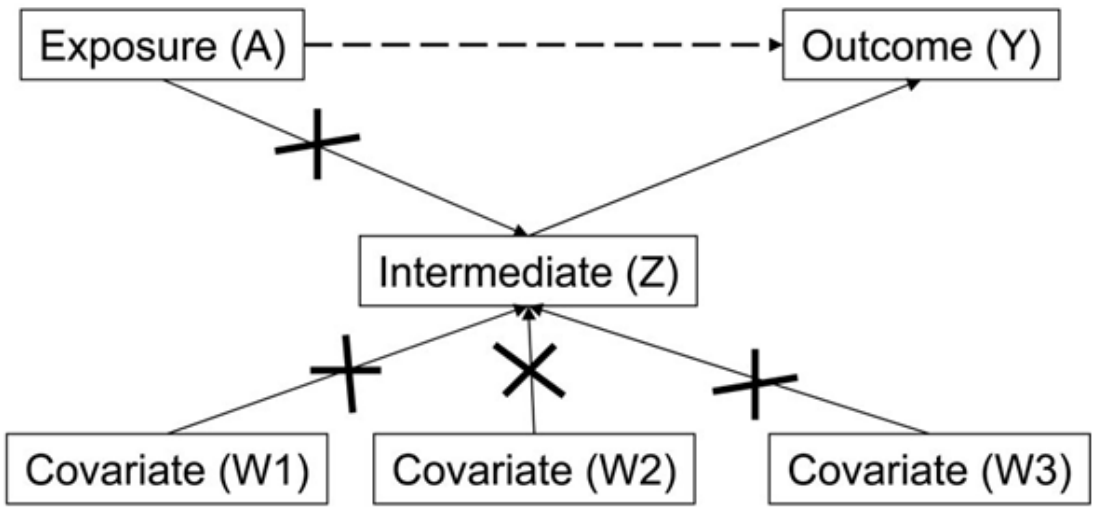
Controlled direct effects

Controlled direct effect: $Y_{xm} - Y_{x^*m}$

- *contrast between the counterfactual outcome if the individual were exposed to X=x and the counterfactual outcome if the same individual were exposed to* $X = x^*$ *with the mediator set to a fixed level M=m*

- Intuitively it corresponds to a situation in which an hypothetical intervention controls the mediator to a given value $\rightarrow$ many controlled direct effects as levels of mediator

Controlled direct effects[1]



[1] Petersen et al. Am J Epid 2006; 17-276-284

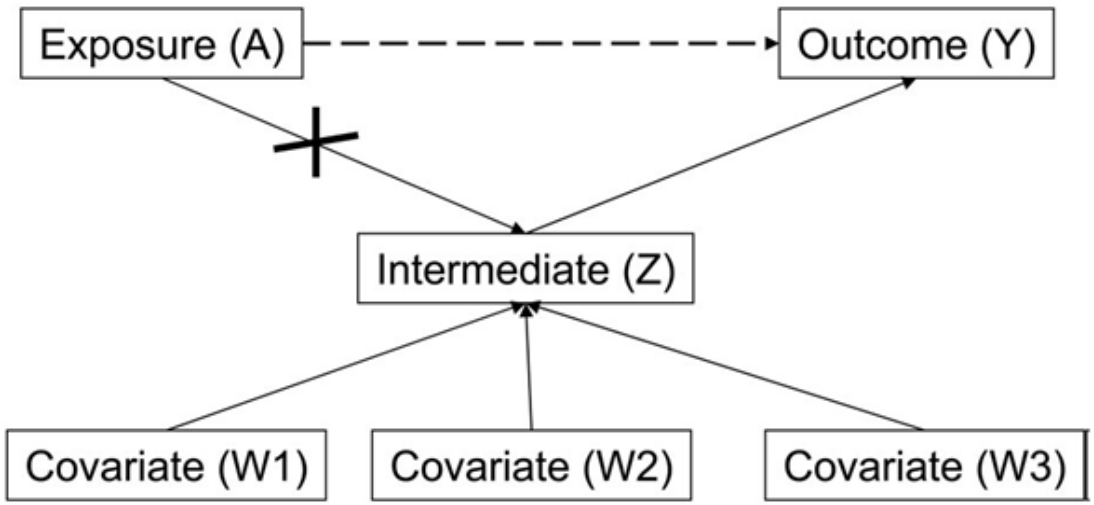
Natural direct effect

Natural direct effect: $Y_{xM_{x^*}} - Y_{x^*M_{x^*}}$

- *contrast between the counterfactual outcome if the individual were exposed to X=x and the counterfactual outcome if the same individual were exposed to* $X = x^*$ *with the mediator assuming whatever value it would have taken at the reference value of the exposure* $X = x^*$

- Intuitively it captures the effect of X on Y via pathways that don't involve M, although M is allowed to vary among individuals according to all determinants of M, with exception of X (intervention on X but not directly on M, the natural relationship between X and M is maintained)

Natural direct effect [2]



[2] Petersen et al. Am J Epid 2006; 17-276-284

Natural indirect effect

Natural indirect effect: $Y_{xM_x} - Y_{xM_{x^*}}$

- *Contrast between the counterfactual outcome if, having set the exposure at level X=x, between the counterfactual outcome if the mediator assumed whatever value it would have taken at a value of the exposure $X = x$ and the counterfactual outcome if the mediator assumed whatever value it would have taken at a reference value of the exposure $X = x^*$*

- Intuitively it captures the effect of X on Y due to the effect of X on M

Natural and controlled direct effects

- CDE, NDE, NIE cannot be estimated at the individual level, but on average for a population under specific assumptions
- In absence of exposure-mediator interaction, controlled and natural direct effect are equivalent (note: this is not a test)
- In presence of exposure-mediator interaction, natural direct effect represent a sort of interpretable population average over the levels of mediator: they are calculated as a weighted average of the controlled direct effects at each level of mediator with the weight given by the probability that the mediator would have taken that level if the exposure were set at its reference level

$$NDE(x) = \sum_{m} [E(Y_{xm}) - E(Y_{x^*m})] Pr(M_{x^*} = m)$$

Example

X	M	Risk	Cases	Non-cases	Total
0	0	1%	100	9900	10000
1	0	3%	150	4850	5000
0	1	2%	10	490	500
1	1	20%	200	800	1000

Total effect: 4.8% (adjusted for M: 2.3%)
CDE(M=0)=2%
CDE(M=1)=18%
NDE=2%*(1-4.76%)+18%*(4.76%)=2.8%
NIE=4.8%-2.8%=2.0%

Decomposition of TE

- If exposure-mediator interaction exists, natural direct effect and natural indirect effect still sum up to the total effect
  $E(Y_{xM_{\boldsymbol{x}}}) - E(Y_{x^*M_{\boldsymbol{x}^*}}) = E(Y_{xM_{\boldsymbol{x}^*}} - Y_{x^*M_{\boldsymbol{x}^*}}) + E(Y_{xM_{\boldsymbol{x}}} - Y_{xM_{\boldsymbol{x}^*}})$
  TE=NDE+NIE

- The decomposition holds even where there are interactions and nonlinearities

- If exposure-mediator interaction exists, the estimate of total effect, as well as natural direct and indirect effects, depends on the population prevalence of the mediator, i.e. is population-specific

Example[3]

- A drug (X) could induce headache as a side-effect, and, at the same time, could interact with the aspirin (M) taken to treat the drug-induced headache on its effects on the outcome (Y)
- The producer of the drug manages to eliminate headache as a side-effect, and would like to know what the effect of the drug will be in the population (use of the drug will no longer be a cause of aspirin intake)
- Let us suppose that the drug works only if it is taken together with aspirin so that CDE (aspirin=1) = 0.5, CDE (aspirin=0) = 1.0
- In a population where nobody takes the aspirin for other reasons than drug-induced headache the NDE is 1.0
- In a population where half of the unexposed subjects take the aspirin the NDE is 0.75

[3] Modified by Pearl J. san Francisco, CA: Morgan Kauffman, 2001

Decomposition of TE on risks ratio scale

Y dichotomous:

$$RR^{CDE}(m) = \frac{P(Y_{xm})}{P(Y_{x^*m})}$$

$$RR^{NDE} = \frac{P(Y_{xM_{x^*}})}{P(Y_{x^*M_{x^*}})}$$

$$RR^{NIE} = \frac{P(Y_{xM_x})}{P(Y_{xM_{x^*}})}$$

$$\frac{P(Y_x)}{P(Y_{x^*})} = RR^{TE} = RR^{NDE} * RR^{NIE}$$

Decomposition of TE on odds ratio scale

$$OR^{CDE}(m) = \frac{(P(Y_{xm})/(1-P(Y_{xm}))}{(P(Y_{x^*m})/(1-P(Y_{x^*m}))}$$

$$OR^{NDE} = \frac{(P(Y_{xM_{x^*}})/(1-P(Y_{xM_{x^*}}))}{(P(Y_{x^*M_{x^*}})/(1-P(Y_{x^*M_{x^*}}))}$$

$$OR^{NIE} = \frac{(P(Y_{xM_x}))/(1-P(Y_{xM_x}))}{(P(Y_{xM_{x^*}})/(1-P(Y_{xM_{x^*}}))}$$

$$OR^{TE} = OR^{NDE} * OR^{NIE}$$

Alternative decomposition of TE

- In presence of interaction there are two components of the exposure effect:
  1. the exposure affects the mediator and thus the outcome
  2. the exposure, by affecting the mediator, increases also the effect attributable to the exposure-mediator interaction

- Alternative decompositions of total effect can be considered depending on how to account for the interaction

Alternative decomposition of TE[4]

- $E(Y_{xM_x} - Y_{x^*M_{x^*}}) = E(Y_{xM_{x^*}} - Y_{x^*M_{x^*}}) + E(Y_{xM_x} - Y_{xM_{x^*}})$

  TE=PDE+TIE
  Natural direct effect is called pure direct effect
  Natural indirect effect is called total indirect effect

- $E(Y_{xM_x} - Y_{x^*M_{x^*}}) = E(Y_{xM_x} - Y_{x^*M_x}) + E(Y_{x^*M_x} - Y_{x^*M_{x^*}})$

  TE=TDE+PIE
  Natural direct effect is called total direct effect
  Natural indirect effect is called pure indirect effect

- Total effect picks up the interaction, pure effect does not pick up the interaction

[4] Vanderweele, Epidemiology 2013, 224-231

Three-way decomposition of TE

X binary, M binary

$$(Y_{1M_1} - Y_{0M_0}) = (Y_{1M_0} - Y_{0M_0}) + (Y_{0M_1} - Y_{0M_0}) + (Y_{11} - Y_{10} - Y_{01} + Y_{00})(M_1 - M_0)$$

- $(Y_{1M_0} - Y_{0M_0})$ is the pure direct effect
- $(Y_{0M_1} - Y_{0M_0})$ is the pure indirect effect
- $(Y_{11} - Y_{10} - Y_{01} + Y_{00})$ is the counterfactual measure of additive interaction between the exposure and the mediator on the outcome
- $(M_1 - M_0)$ is the effect of the exposure on the mediator

Mediating interactive effect

$$(Y_{11} - Y_{10} - Y_{01} + Y_{00})(M_1 - M_0)$$

- The interactive effects will be nonzero if and only if:
  1. the exposure has some effect on the mediator ($(M_1 - M_0) \neq 0$)
  2. additive interaction is nonzero: if the effect on the outcome of setting both the exposure and the mediator to present differs from the sum of the effects of having only one of the exposure and the mediator present

- The mediated interactive effect is equal to the difference between the total and pure indirect effects

- The mediated interactive effect is equal to the difference between the total and pure direct effects

Three-way decomposition of TE

- The decomposition applied at the individual counterfactual level can be also defined at population average
- Under specific assumptions, standard regression models can be used to estimate the three effects
- A three-way decomposition of TE holds also for a risks ratio and odds ratio scale
- If the interest is to evaluate what portion of a mediated effect requires the joint operation of the exposure and the mediator, the three-way decomposition may be pursued

Example

What is the extent to which the effect of chromosome 15q25.1 rs8034191 C alleles on lung cancer risk is due to mediation by, or interaction with, cigarettes smoked for day?

- rs8034191 C alleles are known to be associated with both smoking and lung cancer
- There had been debate as to whether the effects on lung cancer were direct or mediated by smoking
- 3-way decomposition to assess how much of the effect is due to interaction

Results

- 1836 cases and 1452 controls from a lung cancer case-control study at Massachussets General Hospital
- Exposure: 2 versus 0 alleles, Mediator: cigarettes per day
- Confounders: sex, age, education, and smoking duration

- $RR^{TE} = 1.77, RR^{DE} = 1.72, RR^{IE} = 1.014, RERI = 0.036$

- For the excess relative risk for TE, 93.7% ((1.72-1)/(1.77-1)) is attributable to the pure direct effect, 1.7% ((1.014-1)/(1.77-1)) is attributable to pure indirect effect and 4.6% (0.036/0.77) is attributable to the mediated interaction

- Of the mediated effect (small proportion: 1.7%+4.6%=6.3%), most of the mediated effect is attributable to the mediated interaction rather than a pure indirect effect

Four-way decomposition of TE[5]

X binary, M binary

$$(Y_{1M(1)} - Y_{0,M(0)}) = (Y_{10} - Y_{00}) + (Y_{11} - Y_{10} - Y_{01} + Y_{00})(M_0)$$
$$(Y_{11} - Y_{10} - Y_{01} + Y_{00})(M_1 - M_0) + (Y_{01} - Y_{00})(M_1 - M_0)$$

- first component is the direct effect of X if M were removed (CDE)(due neither to mediation nor interaction)
- second component is the additive interaction that operates only if M is present in absence of X (interaction only)
- third component is the additive interaction that operates only if X has an effect on M (mediation and interaction)
- fourth component is the pure indirect effect (mediation only)

[5] Vanderweele, Epidemiology 2014; 25: 749-761

Results

Component	Excess RR	95% CI	Proportion attr.	95% CI
No mediation, no interaction	0.30	-0.19-0.79	39%	-11%-89%
Interaction	0.42	0.11-0.73	55%	8%-101%
Mediation, interaction	0.034	-0.02-0.09	4%	-3%-11%
Mediation	0.014	-0.01-0.04	2%	-1%-5%
Total	0.77	0.33-1.21	100%	

- Overall proportion due to mediation: (0.014+0.034)/0.77=6%
- Overall proportion due to interaction: (0.42+0.034)/0.77=59%
- Mediation may play a role but interaction is clearly much more important

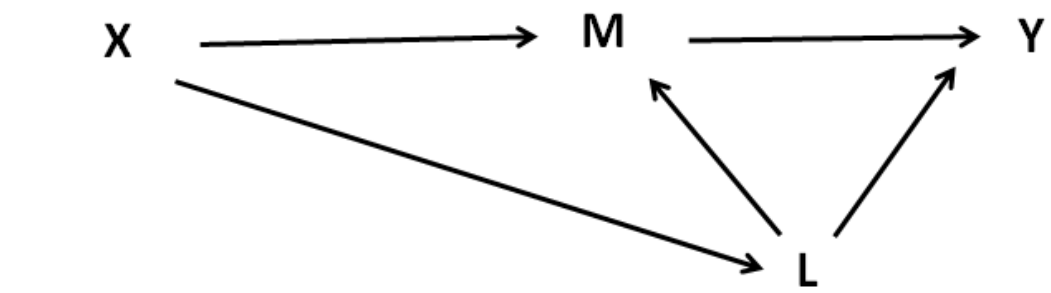
Mediation decompositions

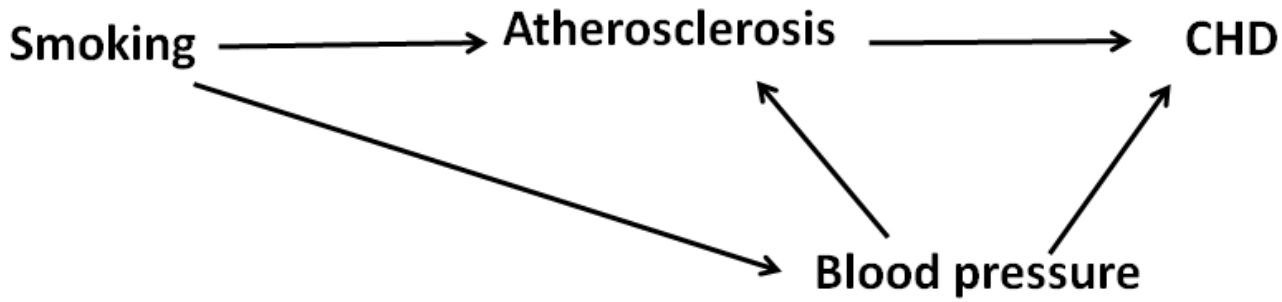
Components	Decomposition
Two-way	$TE = PDE + TIE$
Two-way	$TE = TDE + PIE$
Three-way	$TE = PDE + PIE + INT_{med}$
Four-way	$TE = CDE + INT_{ref} + INT_{med} + PIE$

Components	Decomposition
Two-way	$(1.77 - 1) = (1.72 - 1) + (1.05 - 1)$
Two-way	$(1.77 - 1) = (1.756 - 1) + (1.014 - 1)$
Three-way	$(1.77 - 1) = (1.72 - 1) + (1.014 - 1) + 0.036$
Four-way	$(1.77 - 1) = (1.30 - 1) + 0.42 + 0.034 + (1.014 - 1)$

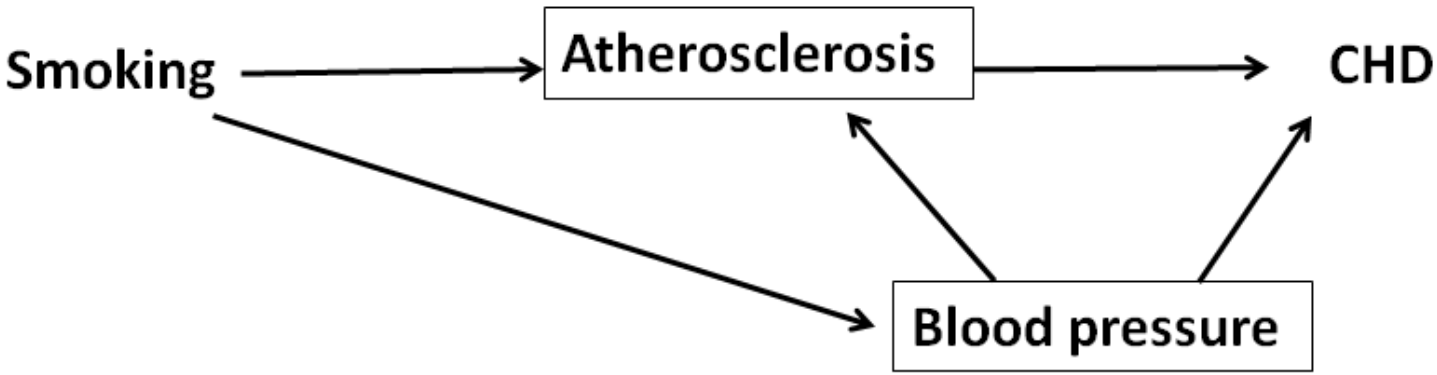
Intermediate confounding

- It is necessary to adjust for mediator-outcome confounding in the standard regression models to avoid collider bias
- There are exceptions:





Example



Adjustment for blood pressure:

- is necessary to prevent collider bias
- would bias the estimate of the direct effect of smoking on CHD acting through blood pressure but not atherosclerosis

Methods

In presence of mediator-outcome confounding affected by the exposure:

- traditional multivariable methods will provide biased estimate of the CDE, NDE and NIE
- CDE can be identified and consistently estimated by alternative methods based on counterfactuals:
  - inverse probability weighting [6] (by regressing Y on X and M and by controlling for confounding by re-weighting the population instead of introducing them in the regression model)
  - G-computation [7](extension of the standardization using Montecarlo simulations)
- NDE and NIE cannot be identified $\rightarrow$ bounds or sensitivity analysis must be applied $\rightarrow$ restriction of contemporary methods to settings in which the mediator occurs shortly after the exposure to minimize the M-Y confounding affected by X

[6] Vanderweele TJ, Epidemiology 2009;20:18-26

[7] Daniel R et al. The Stata Journal 2011;11:479-517

In summary

- To identify controlled direct effects:
  1. lack of unmeasured/unkown exposure-outcome confounding
  2. lack of unmeasured/unkown mediator-outcome confounding

- To identify natural direct and indirect effects:
  1. (1) and (2)
  2. lack of unmeasured/unkown exposure-mediator confounding
  3. lack of unmeasured/unkown mediator-outcome confounding affected by the exposure

Consistency and composition assumptions are also needed to relate the observed data to counterfactual quantities. Consistency assumption is that when $X = x$, the counterfactuals Y_x, M_x are equal to the observed Y, M, and when $X = x, M = m$, the counterfactual Y_{xM_x} is equal to Y. Composition assumption is that $Y_x = Y_{xM_x}$.

Example

In cancer epidemiology, large disparities exist in stage at diagnosis and cancer-related mortality among different ethnicities and socioeconomic groups, for example due to:

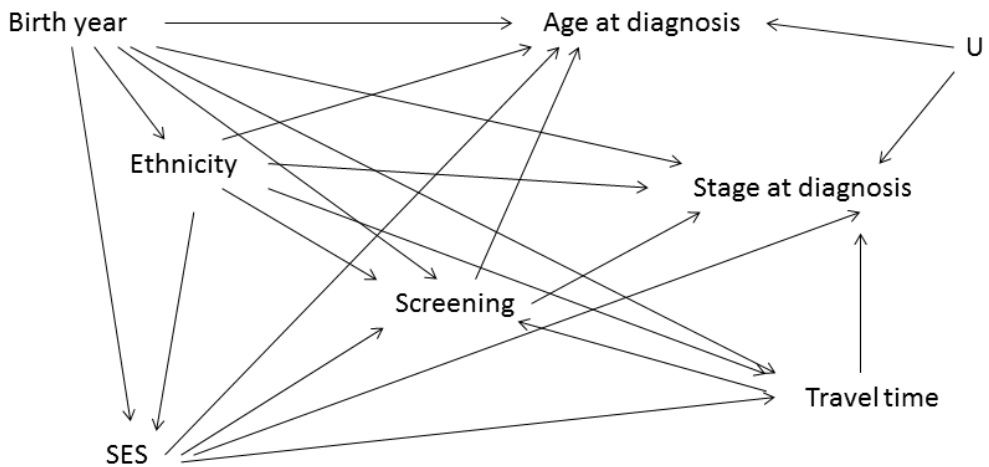
- differences in screening patterns
- patterns of treatment
- benefit income
- employment
- household income
- home ownership
- geographical access to health services
- cultural and genetic factors

Questions of interest

- How much of the causal effect of ethnicity on stage at diagnosis of cancer is mediated/unmediated by the adherence to screening?
- How much of the causal effect of ethnicity on cancer mortality is mediated/unmediated by the diagnosis at later stage?
- What would happen if everybody were screened or were diagnosed at early stage?

Study population[8]

1455 cervical cancer cases recorded in the New Zealand Cancer Registry (NZCR) between 1 January 1994 and 30 December 2005: 1163 women were European and 292 were Maori



How much of the effect of being Maori *vs* European women on stage at diagnosis acts through the adherence to screening?

[8] Brewer, Zugna et al. Cancer Epidemiology 2012

Results

Standard regression adjusted for	OR	95% CI	RD	95% CI
birth year	2.69	1.99,3.62	0.17	0.12,0.23
birth year and screening status	2.43	1.80,3.29	0.14	0.09,0.20

	g-formula		IPTW		IPTW no interaction	
Effects	Estimates	95% CI	Estimates	95% CI	Estimates	95% CI
TCE	0.16	0.10,0.23	0.16	0.09,0.22	0.15	0.09,0.22
NDE	0.14	0.08,0.21	0.13	0.05,0.20	0.13	0.07,0.20
NIE	0.02	-0.02,0.05	0.03	0.01,0.05	0.02	0.01,0.03
CDE	0.14	0.04,0.23	0.04	-0.07,0.15	0.11	0.05,0.18

MSM	g-formula		IPTW	
OR	Estimates	95% CI	Estimates	95% CI
Ethnicity	2.20	1.68,2.94	2.05	1.35,2.53
Screened	0.45	0.33,0.61	0.46	0.34,0.62

Conclusions

- Maori women were at higher risk to be diagnosed at later stage than European women, and this risk was mostly not attributable to their screening history
- Effects estimated by standard regression will differ from effects estimated by g-computation formula/IPTW as much as the exposure and the mediator interact and there are mediator-outcome confounders affected by the exposure
- IPTW is known to be less precise and more unstable than g-computation formula. This difference in efficiency may explain the higher sensitivity of IPTW to the inclusion/exclusion of the interaction term in MSM