

Mediation analysis

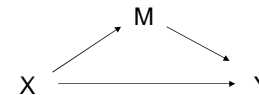
Often research questions in epidemiology are concerned with the pathways (mechanisms) by which an exposure affects the outcome

- molecular epidemiology
- social epidemiology
- life-course epidemiology

Typical questions

- How much of socioeconomic differences in incidence of cardiovascular diseases are mediated by individual risk factors?
- How much of the effect of SES in childhood on adult disease is mediated by SES in adulthood?
- How much of the effect of smoking on cardiovascular disease is mediated by inflammation?

Simplest situation

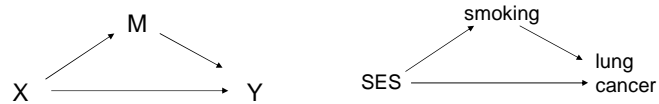


The aim is to distinguish between:

- the path $X \rightarrow M \rightarrow Y$: **indirect effect**
- the path $X \rightarrow Y$: **direct effect**

i.e. To what extent the total effect of the exposure E on the outcome Y is explained or is not explained by a given set of hypothesized mediators?

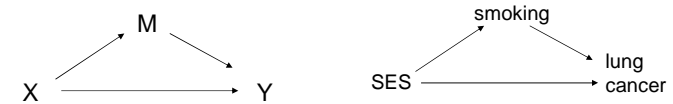
Traditional approach (1)



→ To estimate the effect of X on Y for a given value of M (e.g. M=0) and to interpret it as the direct effect of X on Y

→ For example, if X is SES, M is smoking and Y is lung cancer the effect of SES on lung cancer in non-smokers would be interpreted as the direct effect of SES on lung cancer (i.e. the effect of SES that is not explained by smoking)

Traditional approach (2)



→ to fit a regression model with Y as the outcome and X as the explanatory variable (total effect)

→ to add M as a covariate in the model (direct effect)

→ if the coefficient of X changes from the adjusted (A) to the unadjusted (U) model, there is evidence of mediation.

% excess risk explained by the mediator:
 $(RR_U - RR_A) / (RR_U - 1) * 100$

Example

- Study on SES (low vs. high) and lung cancer
- Crude RR = 2.3 (Total effect)
- RR adjusted for smoking and diet = 1.2 (direct effect?)
- %Excess risk = $(2.3 - 1.2) / (2.3 - 1) = 85\%$

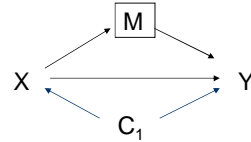
(Note: it is theoretically possible to have no total effect in presence of opposite direct and indirect effects –unfaithfulness)

Issues

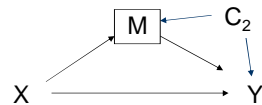
- This approach to mediation analysis may produce biased results.
- The main issues are:
 - Mediator-outcome confounding
 - Presence of exposure-mediator interaction
 - Intermediate confounding

Mediator-outcome confounding

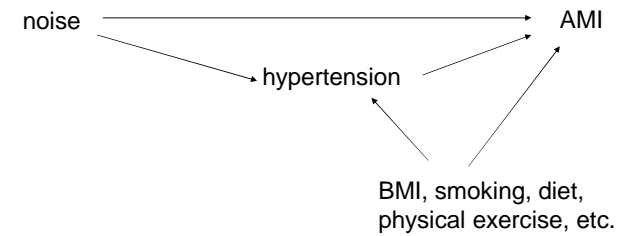
1) X-Y confounding



2) M-Y confounding



Example M – Y confounding



Adjustment for hypertension introduces collider bias

Can this bias be avoided?

Yes!

We should adjust for the M-Y confounders

Quantification of the collider bias

- Greenland 2003; Pizzi 2011; Bakely 2002; Hafeman 2011; Whitcomb; etc.
- Vanderweele 2010

Bias in the direct effect:
$$\frac{[1+(\gamma-1)\pi_a]}{[1+(\gamma-1)\pi_{a^*}]}$$

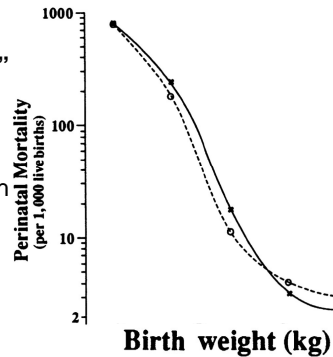
$\gamma \rightarrow$ direct effect of the unmeasured confounder (U) on the outcome

π_a and $\pi_{a^*} \rightarrow$ are the prevalences of the unmeasured confounder among exposed and unexposed subjects for a given value of the mediator

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

Low birth weight “paradox”

crossover of birth weight specific mortality: smoking seems to be beneficial among low birth weight babies



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

Collider bias

VanderWeele et al

Epidemiology • Volume 23, Number 1, January 2012

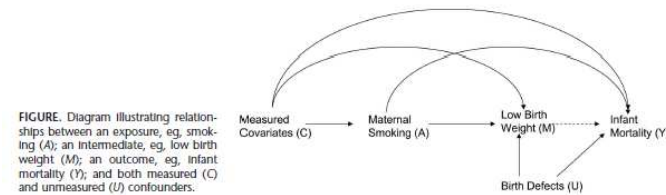


FIGURE. Diagram illustrating relationships between an exposure, eg, smoking (A); an intermediate, eg, low birth weight (M); an outcome, eg, infant mortality (Y); and both measured (C) and unmeasured (U) confounders.

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)

Direct effect of 0.79 for M=1 (low bw)

Can collider bias explain a RR of 0.79? Let's assume

Direct RR of infant mortality for birth defects: 3.5

For infants with low birth weight:

→ Prev of birth defects in infants with no maternal smoking = 2.5%

→ Prev of birth defects in infants with maternal smoking = 14%

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

Back to the example of SES and lung cancer

Crude RR: 2.3; Adjusted RR: 1.2. Let's assume

Direct RR of lung cancer for positive family history: 2.5

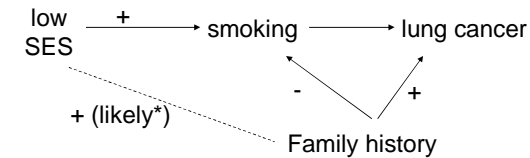
Among, say, non smokers:

→ Prev of family history in low SES men= 20%

→ Prev of family history in high SES men: 5%

$$\frac{1+(2.5-1)(0.20)}{1+(2.5-1)(0.05)} = 1.2$$

Note



* If there are interactions or non-linear association involved this rule may not apply

Exposure-mediator interaction

Hypothetical data

E	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

TE = 4.8% M-adjusted effect = 2.3%

DE (M=0) = 2%

DE (M=1) = 18%

Thus

- If there is exposure-mediator interaction, the **direct effect** can be different for each value of the mediator
- The **total effect (TE)** is the same, irrespective of the mediator
- How can we decompose the total effect into direct and indirect effects?

We need an alternative definition

Using the **counterfactual framework** we can define:

Controlled direct effects (CDE)

Natural direct effects (NDE)

Natural indirect effects (NIE)

Total and controlled direct effects under the counterfactual framework

If Y_{am} is the potential outcome for both the exposure A and the mediator M and there are two exposure levels, a and a^*

Total causal effect: $E(Y_{a, m(a)} - Y_{a^*, m(a^*)})$

“contrast between the counterfactual outcome under the exposure (including the value that the mediator would take under the exposure) and the counterfactual outcome under no exposure”

Controlled direct effect: $E(Y_{a, m} - Y_{a^*, m})$

“contrast between the counterfactual outcome if the individual were exposed at $A=a$ and the counterfactual outcome if the same individual were exposed at $A=a^*$, with the mediator set to a fixed level m”

Natural direct effect

Natural direct effect: $E(Y_{a, M(a^*)} - Y_{a^*, M(a^*)})$

“contrast between the counterfactual outcome if the individual were exposed at $A=a$ and the counterfactual outcome if the same individual were exposed at $A=a^*$, with the mediator assuming whatever value it would have taken at the reference value of the exposure $A=a^*$ ”

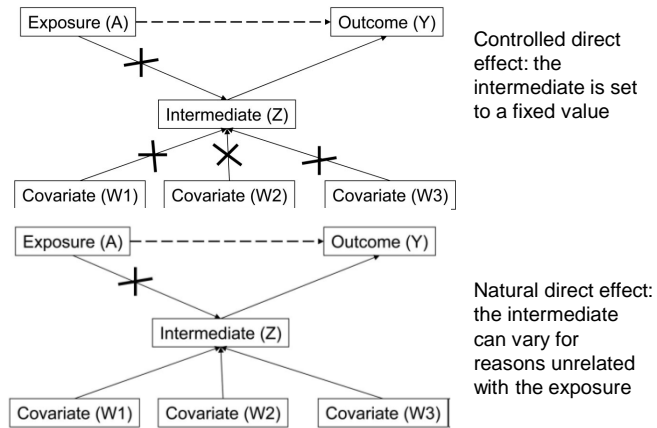
Natural indirect effect: $E(Y_{a, M(a)} - Y_{a, M(a^*)})$

“contrast, having set the exposure at level $A=a$, between the counterfactual outcome if the mediator assumed whatever value it would have taken at a value of the exposure $A=a$ and the counterfactual outcome if the mediator assumed whatever value it would have taken at a reference value of the exposure $A=a^*$ ”

Interpreting CDE and NDE (1)

- A controlled direct effect corresponds to a situation in which a hypothetical intervention controls the mediator to a given value
- A natural direct effect corresponds to a situation in which the natural relationship between the exposure and the mediator is maintained (i.e. we would intervene on the exposure but not directly on the mediator).
- If there is no E-M interaction $CDE=NDE$
- If there is E-M interaction, the natural direct effect represent a sort of interpretable population average over the levels of the mediator

Interpreting CDE and NDE (1)



Petersen et al. Am J Epidemiol 2006;17:276-284

Hypothetical example

E	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

TE = 4.8% M-adjusted effect = 2.3%

CDE (M=0) = 2%

CDE (M=1) = 19%

NDE = 2.8%

NIE = 4.8% - 2.8% = 2.0%

NDE → average between 2% and 19% weighted by the frequency of the mediator among the unexposed: $[2\% * (1 - 4.76\%) + 18\% * (4.76\%)] = 2.8\%$

Advantage of the NDE

- Decomposition of the **total causal effect** into natural direct and **natural indirect effect** is possible:

$$\text{NDE} + \text{NIE} = \text{TDE}$$

$$Y_{a,M(a^*)} - Y_{a^*,M(a^*)} + Y_{a,M(a)} - Y_{a^*,M(a)} = Y_{a,M(a)} - Y_{a^*,M(a)}$$

Example of use of NDE

- a drug (E) 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
- 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

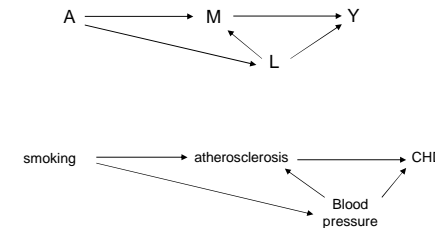
Modified from Pearl J. San Francisco, CA: Morgan Kaufmann, 2001

On the interaction

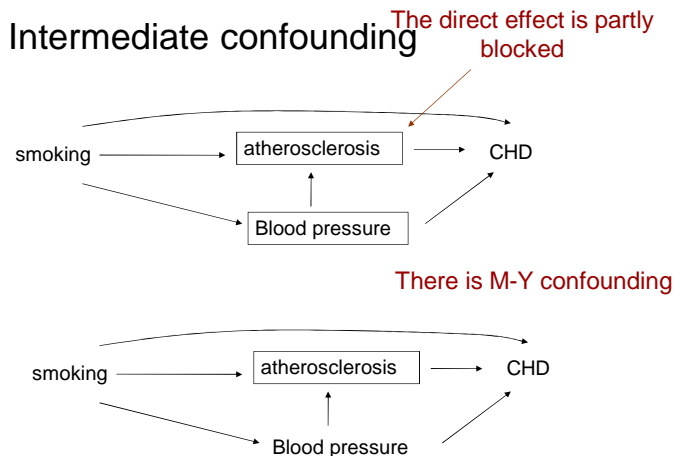
- NDE differs from the CDE because there is interaction between the exposure and the mediator (note: this is not a test)
- This should be taken into account when interpreting the NIE. In presence of interaction there are two components of the NIE
 - the exposure affects the mediator and thus the outcome
 - the exposure, by affecting the mediator, increases also the effect attributable to the exposure-mediator interaction
- There are alternative ways to decompose the total effect: e.g. *pure* direct, *pure* indirect and interactive
- According to these definitions, the NIE is a total indirect effect that includes the pure indirect effect and the interactive effect

Intermediate confounding

An intermediate confounding is a M-Y confounder that is affected by the exposure.



Intermediate confounding



Methods for mediation analysis

- Based on regression models
- Based on counterfactuals, including:
 - G-computation formula for counterfactual comparisons (see Daniel R et al. The Stata Journal 2011;11:479-517)
 - Inverse probability of treatment-weighted estimation of marginal structural models (see Vanderweele TJ, Epidemiology 2009;20:18-26)
- A number of assumptions are still required but these methods can estimate natural direct and indirect effects and deal with intermediate confounding

Example

Background

There are substantial ethnic inequalities, stage at diagnosis and cervical cancer survival in New Zealand

Several factors may play a role in generating these differences:

- screening practice,
- treatment,
- socioeconomic status,
- access to health services,
- cultural and genetic factors.

Study population

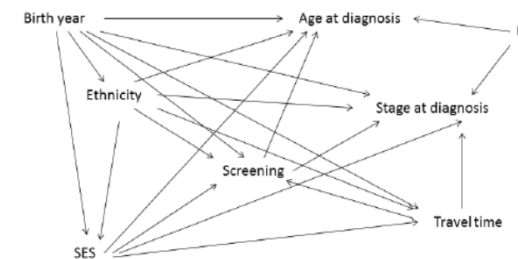
➤ 1204 cervical cancer patients, Maori or of European origin, registered in the New Zealand Cancer Registry (NZCR) between Jan 1994 and Dec 2005 and followed-up until Dec 2007

➤ Information on socio-economic status (score based on the residential area as recorded in the NZCR), travel time to nearest general practitioner (GP) and cancer centre, screening history (National Cervical Screening Programme Register), stage at diagnosis (NZCR), comorbid conditions and mortality (hospital events data from National Minimum Dataset).

RESULTS (Brewer et al 2010 and 2011):

Ethnic differences in stage at diagnosis are not entirely explained by differences in screening history

Increased risk of mortality in Maori compared to women of European origin is only partially explained by adjustment for stage at diagnosis



What proportion of the ethnic differences in stage at diagnosis could not be attributed to differences in screening practices?

Brewer et al. Cancer Epidemiology 2012. Zugna et al. manuscript in preparation

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

Effects	g-formula	
	Estimates	95% CI
TCE	0.16	0.10,0.23
NDE	0.14	0.08,0.21
NIE	0.02	-0.02,0.05
CDE	0.14	0.04,0.23

Comments:

- 1) The higher risk of being diagnosed at a later stage of Maori women compared with women of European origin was not attributable to their screening history
- 2) Consistent estimates between standard regression and G-computation formula

Further examples

