An introduction to mediation analysis

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Something about me

Dr Federico Andreis,

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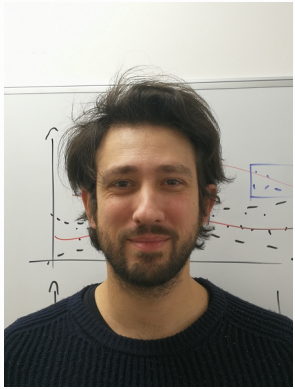
- PhD in Statistics @ University of Milan-Bicocca / Karolinska Institutet, Stockholm
- sampling theory and applications, statistical modelling of electronic health records, non-standard Bootstrap, item response theory



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Plan for the lecture

The course material for these lectures include:

- recording
- lecture slides
- references for further reading.

Learning outcomes

By the end of these lectures, you should be able to:

- describe the main ideas behind mediation analysis
- distinguish between mediation and interaction
- apply basic regression-based mediation methods.

A bit of context

Epidemiology, public health, and clinical research are largely about assessing and explaining exposure-outcome associations.

However:

- assessing association is often only the starting point
- investigating causality may be more relevant to decision-making
- addressing additional questions is therefore required.

Three important aspects

Establishing association does not translate into deep understanding even when a causal association can be established. We want to know:

1. **whether** X affects Y
2. **how** X exerts its effect on Y
3. **when** X affects Y and when not.

$\longrightarrow$ investigating contribution of other factors in the exposure-outcome association.

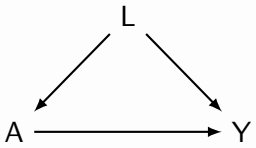
Useful concepts: Directed Acyclic Graphs

Directed Acyclic Graphs (DAG) can be used to overcome problems with traditional covariate selection strategies.

A DAG is a graphical representation of underlying causal structures that:

- encodes our a priori causal knowledge/beliefs
- allows use of simple graphical rules to determine conditioning sets.

A simple DAG

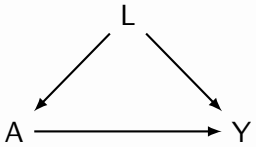


Each arrow represents a causal influence. The graph is

- **Directed**, since each connection between two variables consists of an arrow
- **Acyclic**, since the graph contains no directed cycles

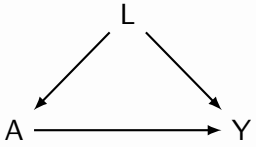
There is a formal connection to potential outcomes/counterfactuals through non-parametric structural equations (beyond the scope of this course).

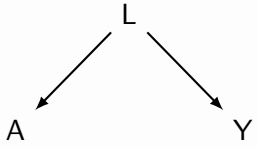
Underlying assumptions



Assumptions are encoded by the direction of arrows: the arrow from A to Y means that A may affect Y, but not the other way around.

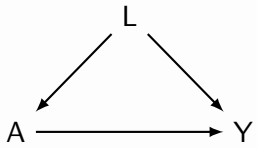
Underlying assumptions, cont'd

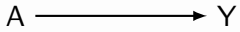




Assumptions are encoded by the absence of arrows: the presence of an arrow from A to Y means that A may or may not affect Y, while its absence means that A does not affect Y.

Underlying assumptions, cont'd

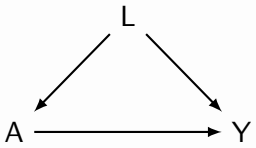




Assumptions about common causes:

- the presence of L means that A and Y may or may not have common causes
- the absence of L means that A and Y do not have any common causes.

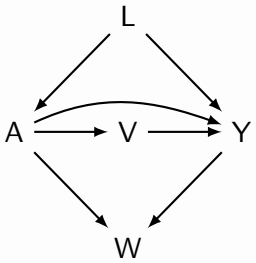
Ancestors and descendents



The **ancestors** of a variable are all other variables that affect it, either directly or indirectly: L is the single ancestor of A

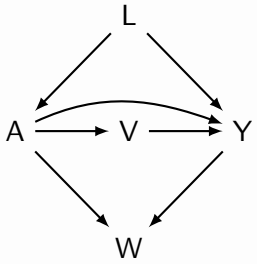
The **descendents** of a variable are all other variables that are affected by it, either directly or indirectly: Y is the single descendent of A.

Paths



A **path** is a route between two variables, not necessarily following the direction of arrows: which are the paths between A and Y?

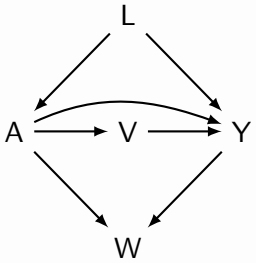
Solution



Four paths exist between A and Y:

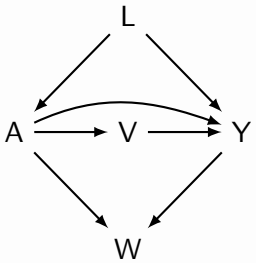
- $A \longrightarrow Y$
- $A \longrightarrow V \longrightarrow Y$
- $A \longleftarrow L \longrightarrow Y$
- $A \longrightarrow W \longleftarrow Y$.

Causal paths



A **causal path** is a route between two variables, **following the direction of arrows**. The causal paths from A to Y **mediate** the causal effect of A on Y, the non-causal paths do not. Which are the causal paths between A and Y?

Solution



There are two causal paths from A to Y:

- $A \longrightarrow Y$
- $A \longrightarrow V \longrightarrow Y$.

An example from health research - HIV and growth

Differences in growth have been reported among children living with HIV.

What we know:

- growth is one of the main predictors of pubertal timing
- delays in pubertal onset and sexual maturity $\longrightarrow$ higher risk of related social and medical outcomes.

What we want to assess:

Is delay in puberty in HIV+ children due to differences in growth? If so, to what extent? (Bellavia et al, 2017)

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Mediation and interaction

Mediation and **interaction** or **moderator analysis** are the statistical tools that address, respectively, our previous points on "**how**" and "**when**":

- mediation: how an effect occurs
- interaction: when/for whom an effect occurs.

Both questions usually require multidisciplinary efforts, given their complexity.

Common applications

- Lifestyle and social factors
- psychology
- interaction between genetic and lifestyle factors
- medical predecessors of common diseases
- epigenetics
- personalised treatments
- . . .

The biological question comes before the statistical one

Statistical methods to assess interaction and mediation (or even confounding), are generally simple/similar.

Correct identification of roles of factors involved in association is crucial.

- DAGs can help conceptualise the causal pathway
- however, failure to identify the correct DAG may lead to severe bias.

Mediation analysis

Mediation analysis investigates the extent to which some variable X influences an outcome Y through one or more *mediator* variables.

Goal: to establish how X exerts its effect on Y.

Postulate model with intervening variable(s) M on the causal pathway between X and Y

The intervening variables are called **mediators**, and are conceptualised as the mechanism by which X causes variation in M, which in turn causes variation in Y.

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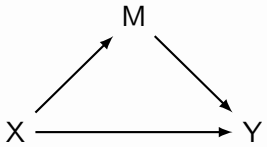

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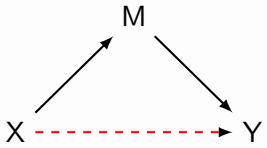
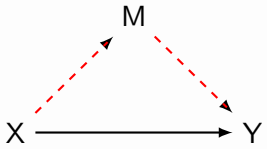
Direct effect

We aim to disentangle the **total effect** of X on Y into a direct effect that goes through all possible pathways but M:



Indirect effect

. . . and an indirect effect that goes through M:



Assessing mediation - continuous outcomes

Classical approach to mediation analysis (Baron and Kenny, 1986):

$$E[Y|x] = \alpha_0 + \alpha_1 x$$
$$E[Y|x, m] = \beta_0 + \beta_1 x + \beta_2 m$$
$$E[M|x] = \gamma_0 + \gamma_1 x$$

$$\text{Direct Effect} = \beta_1$$
$$\text{Indirect Effect} = \alpha_1 - \beta_1 = \beta_2 \gamma_1$$

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Remarks

- Adjusting a model for a mediator $\longrightarrow$ direct effect estimate rather than total. **Crucial to distinguish confounders and mediators!**
- All models can be adjusted for potential confounders
- product=difference statement not always valid (binary and survival outcomes, exposure-mediator interaction, missing values on mediators)
- common summary of mediation model is **proportion mediated (PM)** (only when effects are all in the same direction)

$$PM = \frac{\text{Indirect Effect}}{\text{Total Effect}}$$

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Assessing mediation - binary outcomes

$$\text{logit}P[Y|x] = \alpha_0 + \alpha_1 x$$
$$\text{logit}P[Y|x, m] = \beta_0 + \beta_1 x + \beta_2 m$$
$$E[M|x] = \gamma_0 + \gamma_1 x$$

$$\text{Direct Effect} = e^{\beta_1}$$
$$\text{Indirect Effect} = e^{\beta_2 \gamma_1}$$

Here, equivalence with the difference method only yields when outcome is rare.

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Assessing mediation - survival outcomes

Accelerated failure time models (AFT)

$$\log E[T|x] = \alpha_0 + \alpha_1 x$$
$$\log E[Y|x,m] = \beta_0 + \beta_1 x + \beta_2 m$$
$$E[M|x] = \gamma_0 + \gamma_1 x$$

Proportional hazard model

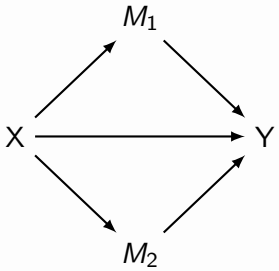
$$h(t|x) = h_0 e^{\alpha_1 x}$$
$$h(t|x,m) = h_0 e^{\beta_1 x + \beta_2 m}$$
$$E[M|x] = \gamma_0 + \gamma_1 x$$

Formulas for direct and indirect effects are the same as for binary outcomes.

Multiple mediators

- Basic approach to two mediators: include an interaction between them and specify two additional statistical models (Vanderweele and Vansteelandt 2013)
- binary and continuous outcomes can be evaluated
- when multiple mediators are of interest, difficult to specify correct statistical models $\longrightarrow$ weighting approaches.

An example DAG



Assessing mediation - multiple mediators

$$
\begin{aligned}
E[Y|x] &= \alpha_0 + \alpha_1 x \\
E[Y|x, m_1, m_2] &= \beta_0 + \beta_1 x + \beta_2 m_1 + \beta_3 m_2 + \beta_4 m_1 m_2 \\
E[M_1|x] &= \gamma_0 + \gamma_1 x \\
E[M_2|x] &= \delta_0 + \delta_1 x \\
E[Z|x] &= \omega_0 + \omega_1 x, \quad \{Z = M_1 M_2\}
\end{aligned}
$$

$$
\begin{aligned}
\text{Direct Effect} &= \beta_1 \\
\text{Indirect Effect through } M_1 \text{ only} &= \beta_2 \gamma_1 \\
\text{Indirect Effect through } M_2 \text{ only} &= \beta_3 \delta_1 \\
\text{Indirect Effect through } M_1 \text{ and } M_2 &= \beta_4 \omega_1
\end{aligned}
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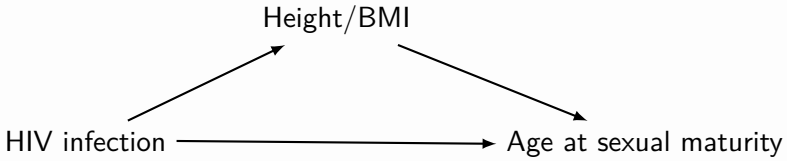
\end{aligned}
$$

Illustrative example - Bellavia et al, 2017

"Delay in Sexual Maturation in Perinatally HIV-Infected Youth Is Mediated by Poor Growth" (Bellavia et al, 2017).

- **Study population**: 2539 children born to HIV-infected mothers.
- **exposure**: HIV status. 453 HIV-exposed uninfected (PHEU) / 2086 HIV-infected (PHIV)
- **mediators**: age- and sex-adjusted z-scores for height and BMI, collected at multiple visits
- **outcome**: pubertal staging assessed by visual inspection (breast development, pubic hair, genitalia)
- confounders were also included.

Illustrative example - a DAG



Illustrative example - modelling

Accelerated Failure Time models with normal distribution for interval-censored outcomes

$$T = \beta_0 + \beta_1 \text{HIV} + \beta_2^T C + \epsilon$$

Where C denotes the confounders.

Linear regression models for height and BMI z-scores, at different time points

$$E[\text{Height}] = \alpha_0 + \alpha_1 \text{HIV} + \alpha_2^T C$$
$$E[\text{BMI}] = \theta_0 + \theta_1 \text{HIV} + \theta_2^T C$$

Illustrative example - multiple mediators

$$
\begin{aligned}
E[T] &= \beta_0 + \beta_1 \text{HIV} + \beta_2^T C \\
E[T] &= \gamma_0 + \gamma_1 \text{HIV} + \gamma_2 \text{Height} + \gamma_3 \text{BMI} + \gamma_4 \text{Height} \cdot \text{BMI} + \gamma_5^T C \\
E[\text{Height}] &= \alpha_0 + \alpha_1 \text{HIV} + \alpha_2^T C \\
E[\text{BMI}] &= \theta_0 + \theta_1 \text{HIV} + \theta_2^T C \\
E[\text{Height} \cdot \text{BMI}] &= \phi_0 + \phi_1 \text{HIV} + \phi_2^T C
\end{aligned}
$$

$$
\begin{aligned}
\text{Total Effect} &= \beta_1 \\
\text{Direct Effect} &= \gamma_1 \\
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\end{aligned}
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Illustrative example - multiple mediators

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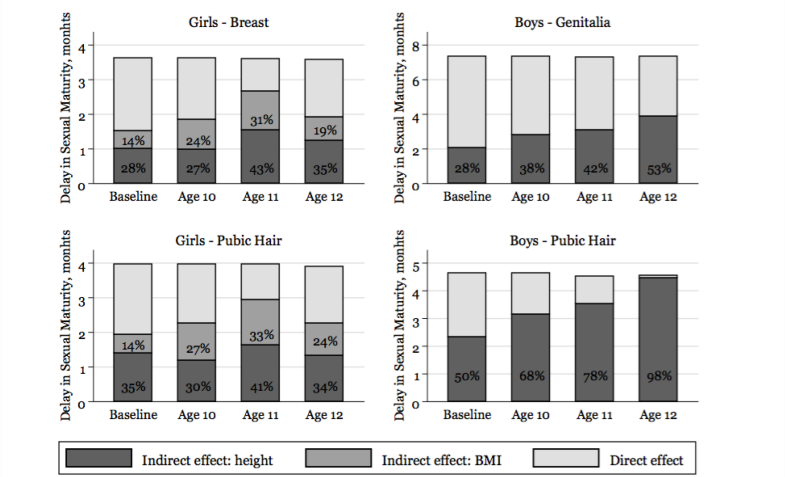
Results - mediation analysis

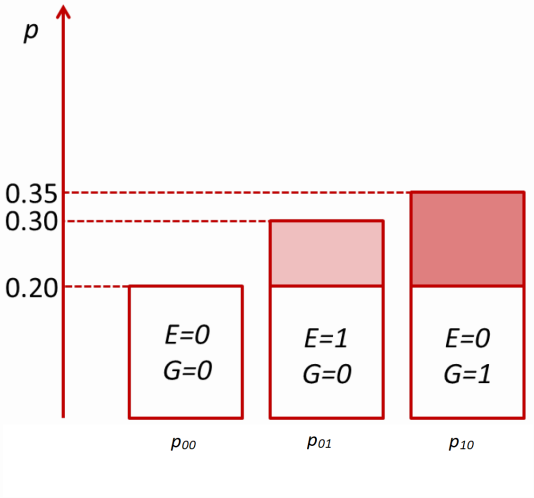


The idea underlying interaction

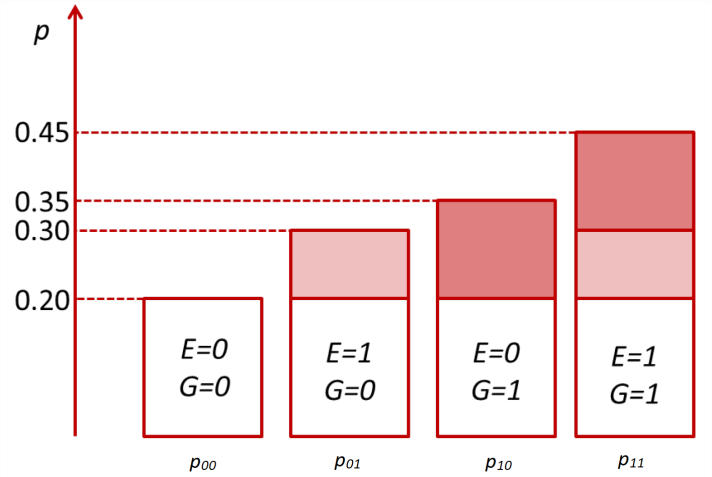
The effect of a given exposure on the outcome may depend on the presence or absence of another exposure.

Suppose we have dichotomous outcome Y and dichotomous exposures G, E.

Let $p_{ge} = P(Y = 1 | G = g, E = e)$.

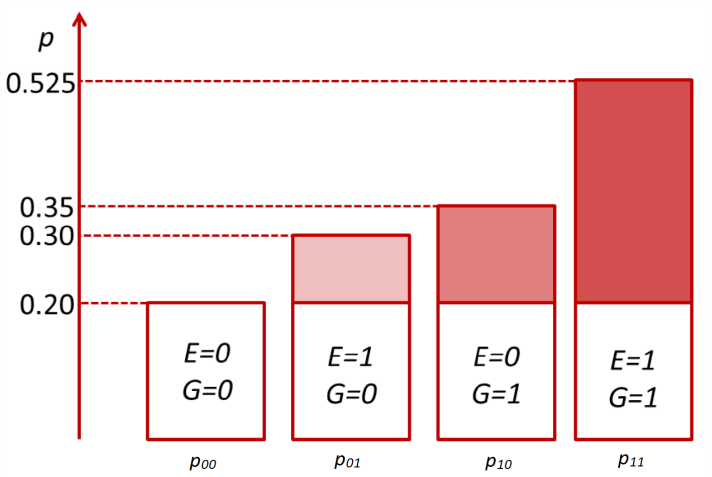


Additive interaction



We say there is **additive interaction** if $p_{11} = p_{10} + p_{01} - p_{00}$.

Multiplicative interaction



We say there is **multiplicative interaction** if $p_{11} = p_{10}p_{01}/p_{00}$.

Interaction - regression models

In a linear model with binary outcome, the regression coefficients are risk differences.

The model is given by:

$$Y \sim \text{Bernoulli}(p_{ge})$$

$$p_{ge} = \beta_0 + \beta_1 g + \beta_2 e + \beta_3 ge$$

β_3 is called the **interaction** term.

Additive interaction

Run through covariate combinations:

$$\begin{aligned}
\mathrm{G} = 0,\ \mathrm{E} = 0;\ & p_{00} = \beta_0 \\
\mathrm{G} = 1,\ \mathrm{E} = 0;\ & p_{10} = \beta_0 + \beta_1 \\
\mathrm{G} = 0,\ \mathrm{E} = 1;\ & p_{01} = \beta_0 + \beta_2 \\
\mathrm{G} = 1,\ \mathrm{E} = 1;\ & p_{11} = \beta_0 + \beta_1 + \beta_2 + \beta_3
\end{aligned}$$

$\longrightarrow \beta_3 = p_{11} - p_{10} - p_{01} + p_{00}$, sometimes called **additive interaction**.

- $\beta_3 > 0$, interaction is positive or super-additive
- $\beta_3 < 0$, interaction is negative or sub-additive.

Multiplicative interaction

In a log-link regression with binary outcome, parameters are linked to risk ratios (RR):

$$\log(p_{ge}) = \beta_0 + \beta_1 g + \beta_2 e + \beta_3 ge$$

Let $\text{RR}_{ge} = \frac{p_{ge}}{p_{00}}$. Running through covariate combinations:

$$\exp(\beta_3) = \frac{p_{11}p_{00}}{p_{10}p_{01}} = \frac{\text{RR}_{11}}{\text{RR}_{10}\text{RR}_{01}}$$

$\exp(\beta_3)$ sometimes called **multiplicative interaction**.

- $\exp(\beta_3) > 1$ termed positive interaction
- $\exp(\beta_3) < 1$ termed negative interaction.

Multiplicative interaction - logistic regression

For logistic regression:

$$\log\left(\frac{p_{ge}}{1-p_{ge}}\right) = \beta_0 + \beta_1 g + \beta_2 e + \beta_3 ge$$

We can formulate the multiplicative interaction using odds ratios (OR):

$$\exp(\beta_3) = \frac{\mathrm{OR}_{11}}{\mathrm{OR}_{10}\mathrm{OR}_{01}}$$

Relative Excess Risk due to Interaction (RERI)

Li and Chambless (2007) proposed the **Relative Excess Risk due to Interaction (RERI)** or **interaction contrast ratio**

$$\text{RERI}_{\text{RR}} = \text{RR}_{11} - \text{RR}_{10} - \text{RR}_{01} + 1$$

Similar to additive interaction but using risks:

- $\text{RERI}_{RR} > 0$
  - positive additive interaction
  - consequences of intervening on E are larger in the $G = 1$ group
- $\text{RERI}_{RR} < 0$
  - negative additive interaction
  - consequences of intervening on E are larger in the $G = 0$ group.

When the outcome is rare, we can use:

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Scale dependence

Interactions are dependent on the outcome model:

- finding an interaction in a particular model does not guarantee to find it in a different model
- switching between risk difference, risk ratio, odds ratio models.

Consider the following table of risks:

p_{ge}	$E=0$	$E=1$
$G=0$	0.02	0.05
$G=1$	0.07	0.10

No additive interaction ($p_{11} - p_{10} - p_{01} + p_{00} = 0.1 - 0.07 - 0.05 + 0.02 = 0$), yet there is negative multiplicative interaction ($\mathrm{RR}_{11}/(\mathrm{RR}_{10}\mathrm{RR}_{01}) = 0.57$).

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A numerical example

Consider the following table of risks:

p_{ge}	$E = 0$	$E = 1$
$G = 0$	0.02	0.05
$G = 1$	0.04	0.10

There is additive interaction ($p_{11} - p_{10} - p_{01} + p_{00} = 0.1 - 0.04 - 0.05 + 0.02 = 0.03$), but no multiplicative interaction ($\mathrm{RR}_{11}/(\mathrm{RR}_{10}\mathrm{RR}_{01}) = 1$).

When reporting interactions **be explicit about the scale** you are using.

Remarks

- Interaction can be defined in different ways (additive, multiplicative)
- the sign of the interaction depends on the chosen scale
- in general, if both exposures have an effect on the outcome, there should be an interaction on some scale
- additive interaction usually the more relevant for public health (it can be used to identify a particular subgroup for intervention).

Remarks - cont'd

- Survival analysis and additive models (Rod et al, 2012; Bellavia et al, 2016)
- interpreting interaction is intuitive with dichotomous exposures, less so with categorical, and challenging with continuous
- there is no agreement on the definition of interaction, neither on the distinction between interaction and effect modification (outside the scope of this course).
- mediation and interaction can occur simultaneously
- causal interpretation is not straightforward: confounding can also operate on mediator-outcome association.

Challenges: exposure-mediator interaction

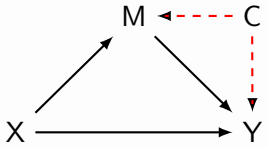
The standard approach to mediation analysis assumes no exposure-mediator interaction. Consider a modelling approach including an interaction term:

$$
\begin{aligned}
E[Y|x] &= \alpha_0 + \alpha_1 x \\
E[Y|x,m] &= \beta_0 + \beta_1 x + \beta_3 xm \\
E[M|x] &= \gamma_0 + \gamma_1 x
\end{aligned}
$$

Here, the previous formulas for direct and indirect effects do not yield valid estimates.

Challenges: mediator-outcome confounding

Confounding can If we do not control for mediator-outcome confounders, then results from the standard approach to mediation can be highly biased.



A famous example: the birth-weight paradox (Hernandez-Diaz et al, 2006).

The counterfactual approach to mediation analysis

The **counterfactual** approach to mediation analysis was introduced to overcome these important limitations (recently summarized in Vanderweele 2015).

Defines direct and indirect effects in terms of the counterfactual intervention: fix exposure and mediator to predefined values (**controlled**), or fix exposure to a predefined value and the mediator to the value that naturally follows (**natural**)

Vanderweele (2014) showed that this way the total effect can be decomposed into four different components:

- direct effect (**controlled**)
- a proportion due to mediation alone (**natural indirect effect**)
- a proportion due to interaction alone (**reference interaction**)
- a proportion due to both mediation and interaction (**mediated interaction**).

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Vanderweele's total effect decomposition

component	interpretation
CDE	treatment effect neither due to mediation nor interaction
INTref	treatment effect only due to interaction
INTmed	treatment effect due to both mediation and interaction
PNIe	treatment effect only due to mediation

Table 1: Components and interpretation of total effect decomposition (Vanderweele, 2014)

Mediation: other relevant extensions

- Causal Mediation Analysis (Robins and Greenland, 1992; Pearl, 2001)
- non-parametric approach (Imai et al, 2010)
- time-varying Exposures and Mediators (van der Laan and Petersen, 2008; Vanderweele, 2009)
- longitudinal analysis (Bind et al, 2017)

Introduction to mediation analysis: wrap-up

- Mediation and interaction analyses are about explaining mechanisms that underline exposure-outcome associations
- interaction provides information on **when/for whom** a given effect occurs
- mediation provides insight on **how** an effect occurs
- recent methodological developments allow evaluating interaction and mediation in a large variety of settings (incl. time-varying and non-modifiable exposure).

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