Causal mediation analysis with multiple mediators

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Joint work with
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Introduction

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designed to prevent heart disease
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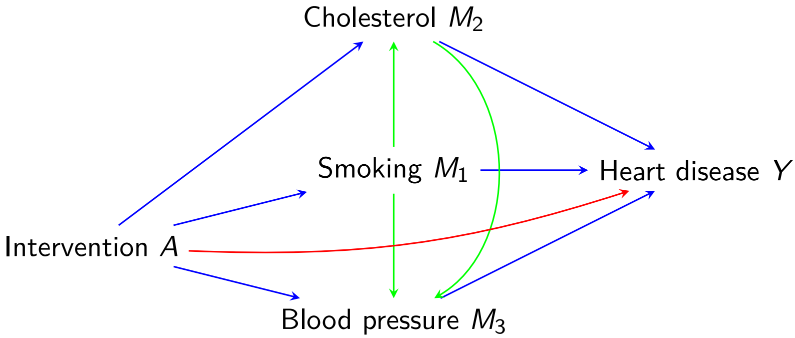
- there may be post-treatment confounding:
  confounders may be mediators at the same time.

  (VanderWeele, Vansteelandt and Robins, 2014)

Multiple mediator models



Can we infer the effect mediated via blood pressure, but not smoking nor cholesterol?

Traditional mediation analysis

- The traditional literature on structural equation models

  (MacKinnon, 2008)

  provides a framework that
  - promises much
  - and is easy to apply.
- But does it deliver?

Critiques on traditional mediation analysis

(Robins and Greenland, 1992; Pearl, 2001; VanderWeele and Vansteelandt, 2009, 2010; Imai et al., 2010)

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- It is vague about interpretation of the effects.
- It is (therefore) vague about validity.

  (consider the problem of adjustment for post-treatment variables)
- It has no justification for nonlinear models.

Counterfactual-based mediation analysis

$$\begin{tikzcd} & \text{Smoking } M \arrow[dr] & \\ \text{Intervention } A \arrow[ur] \arrow[rr] & & \text{Heart disease } Y \end{tikzcd}$$

With a single mediator, important advances have been made with the advent of model-free definitions:

$$\text{natural direct effect :} \quad E\left\{Y(1, M(0))\right\} - \underbrace{E\left\{Y(0, M(0))\right\}}_{E\{Y(0)\}}$$

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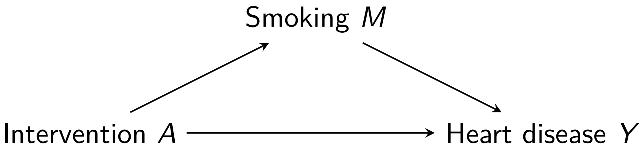

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A corresponding measure of natural indirect effect is obtained as

$$E\{Y(1)\} - E\{Y(0)\} - [E\{Y(1, M(0))\} - E\{Y(0)\}]$$
$$= E\{Y(1, M(1))\} - E\{Y(1, M(0))\}$$

(Robins and Greenland, 1992; Pearl, 2001; VanderWeele and Vansteelandt, 2009, 2010; Imai et al., 2010)

Two decompositions

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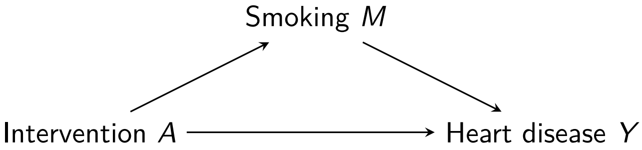

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- Although effect estimands are - unavoidably - complex,
  it is at least clear what they are.
- Many estimation strategies exist,
  some of which are available in software.
- We have a reasonably good understanding of the conditions
  under which these strategies are valid.

When are available strategies valid?

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- *The bad news...:* without making untestable assumptions, real-world experimental data carry no information about natural direct and indirect effects.

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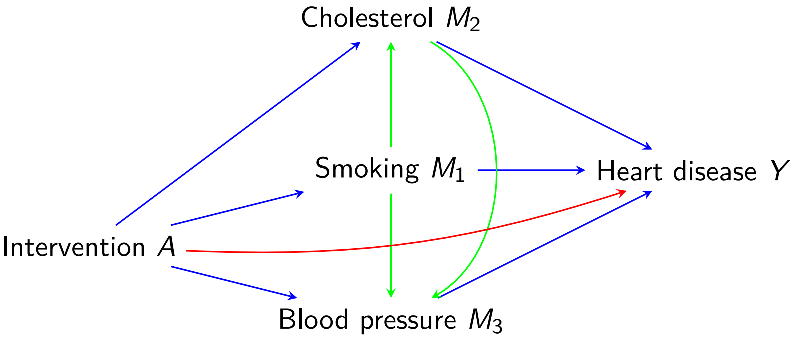
- *The good news...:* valid effects can be obtained if there is a set of variables C that
  - is sufficient to adjust for confounding of the effects of exposure on mediator and outcome;

    this is trivially satisfied when the exposure is randomised.
  - along with A, is sufficient to adjust for confounding of the effect of mediator on outcome;
  - none of those confounders should be affected by exposure.
- The latter makes it difficult to handle multiple mediators.

  (VanderWeele and Vansteelandt, 2013)

Handling multiple mediators is challenging



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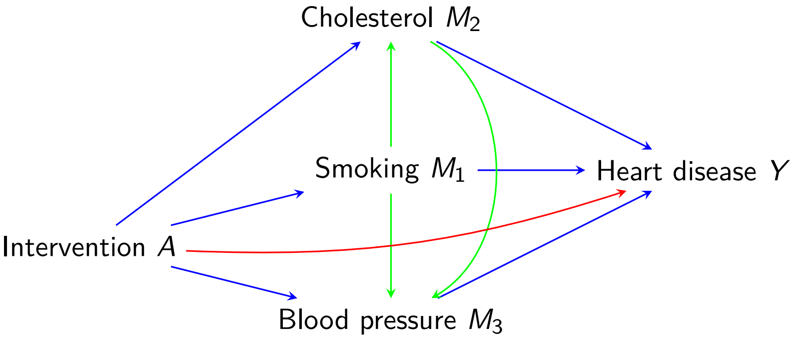
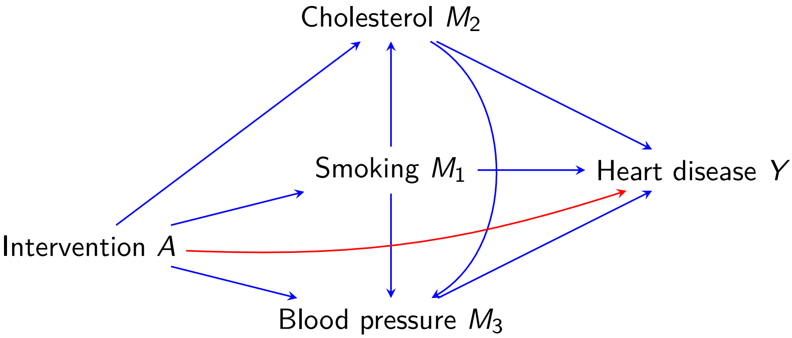


One exception is
when handling multiple mediators 'en bloc'.

Multiple mediator analysis, 'en bloc'



- natural direct effect:

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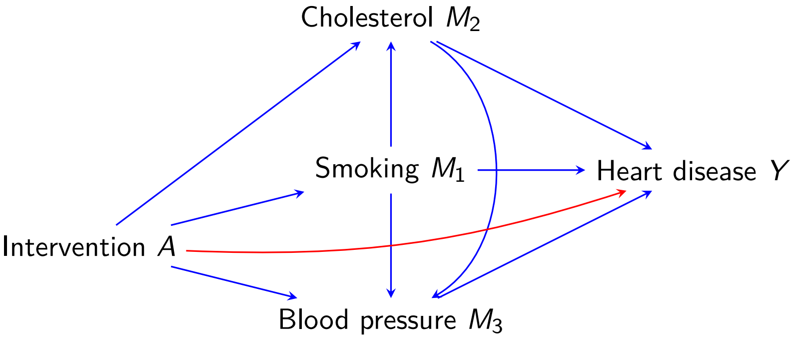

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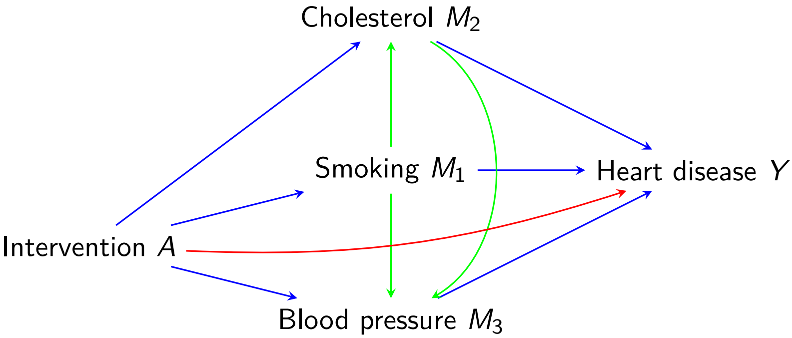
Inferring pathways remains challenging



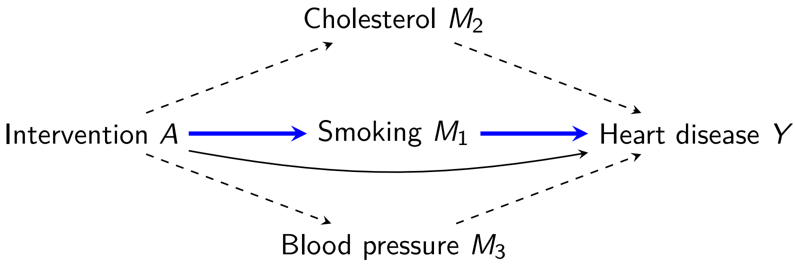
Can we infer the effect mediated via blood pressure, but not smoking nor cholesterol?

Mediation analysis 'one at a time'

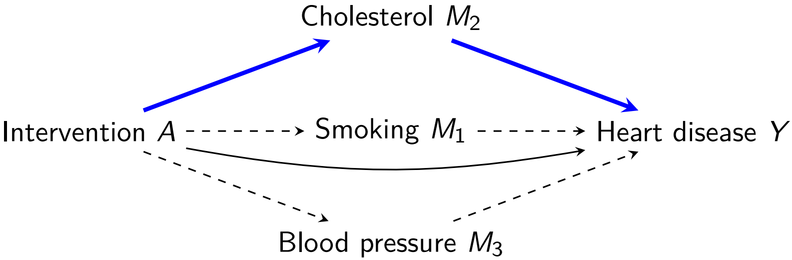
Because inferring pathways is so challenging,
repeated single mediator analyses are quite popular:

- Single mediator analysis with mediator M_1.
- Single mediator analysis with mediator M_2.
- Single mediator analysis with mediator M_3.

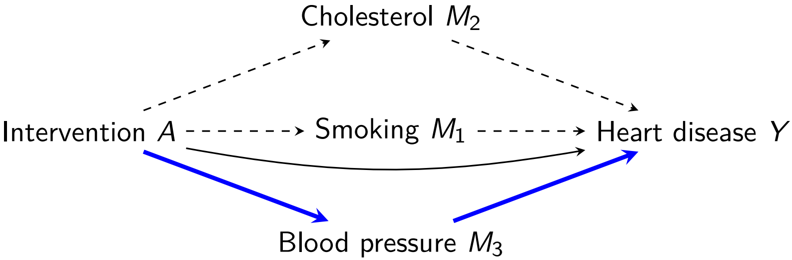
Mediation analysis considering only M_1



Mediation analysis considering only M_2

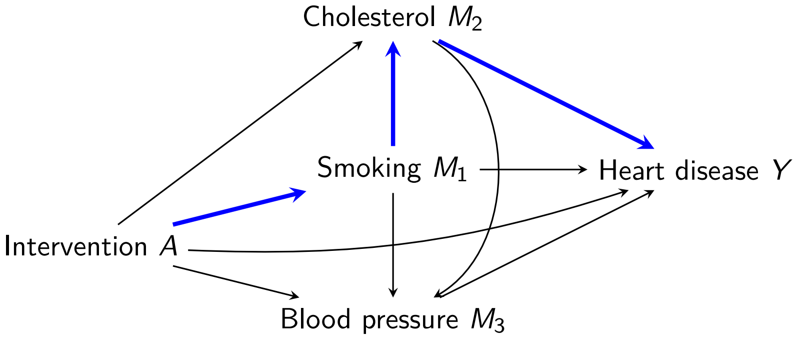


Mediation analysis considering only M_3



Problem 1: no effect decomposition

- The sum of the individual mediated effects may not equal the joint mediated effect.
- This is obvious when the mediators influence one another.



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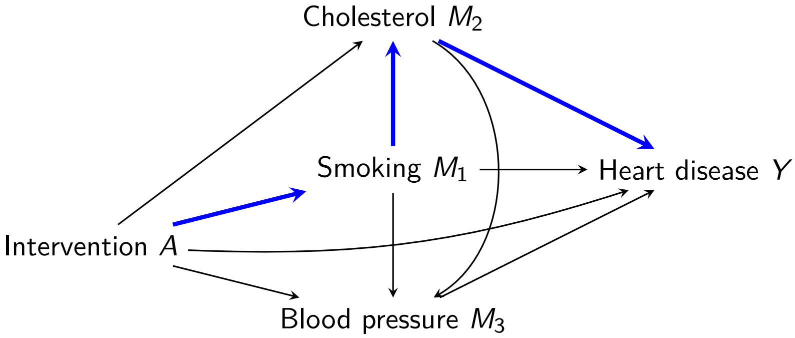
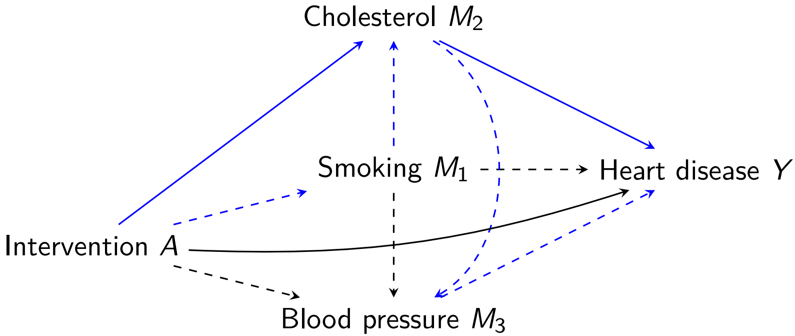


- But it may even happen if the mediators are unrelated, when the mediators interact on the additive scale in the effect they produce on the outcome.

Problem 2: confounding

The effect mediated via M_2 is biased due to confounding by M_1.



Sequential mediation analysis

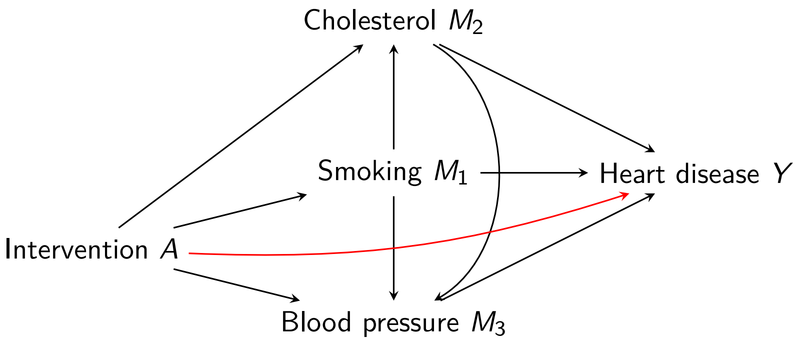
In view of this, we propose sequential mediation analysis 'en bloc':

(VanderWeele and Vansteelandt, 2013)

- Mediation analysis with mediator M_1.
- Mediation analysis 'en bloc' with mediators M_1, M_2.
- Mediation analysis 'en bloc' with mediators M_1, M_2, M_3.

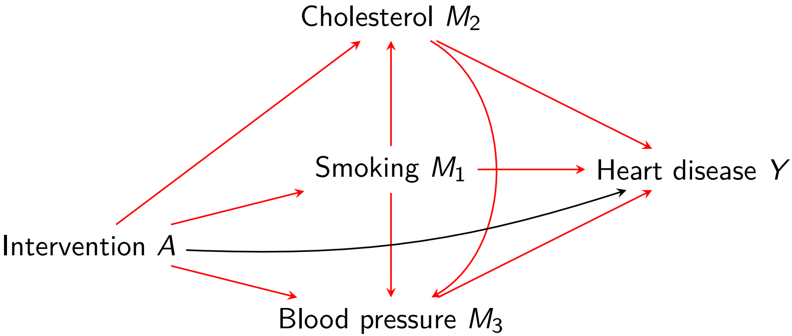
Mediation analysis w.r.t. bloc M_1, M_2, M_3 yields...

... the direct effect



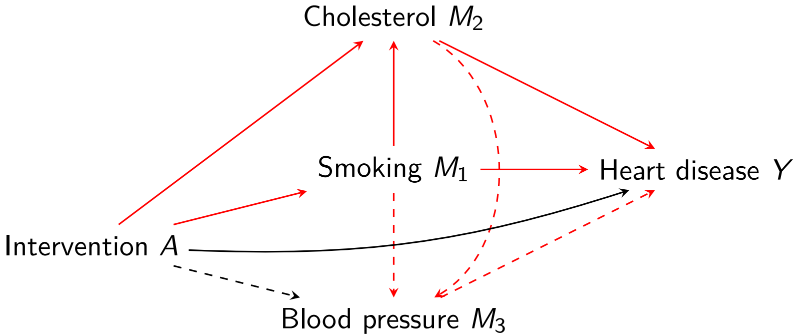
Mediation analysis w.r.t. bloc M_1, M_2, M_3 yields...

... the effect mediated via M_1, M_2 and M_3



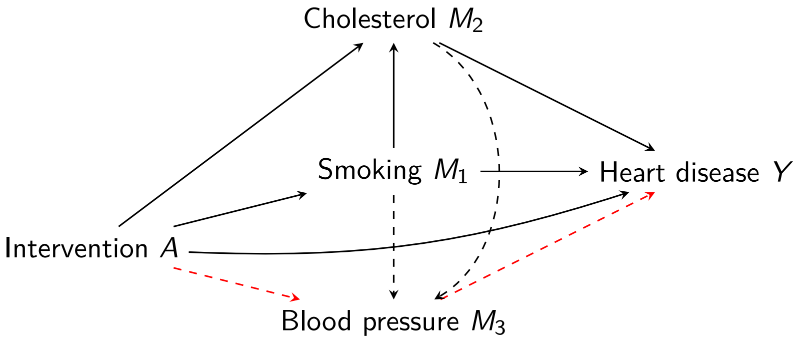
Mediation analysis w.r.t. bloc M_1, M_2 yields...

... the effect mediated via M_1, M_2



Mediation analysis w.r.t. bloc M_1, M_2 yields...

... the effect mediated via M_3, but not M_1, M_2



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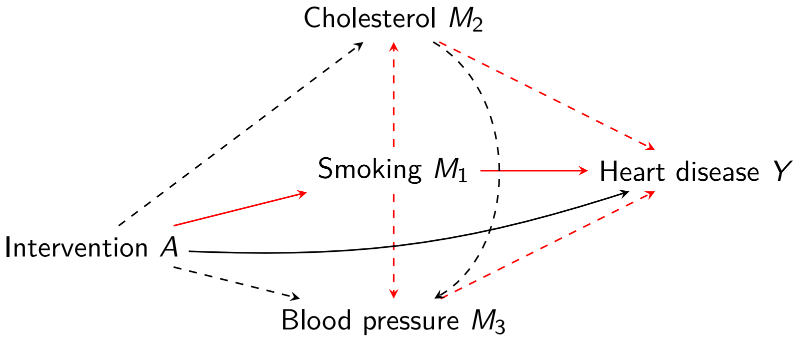
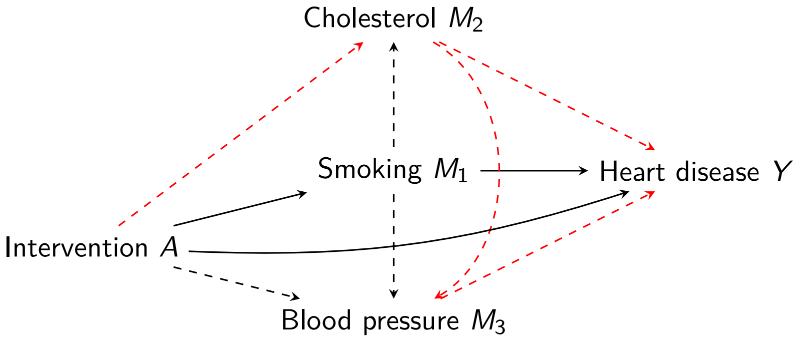


Mediation analysis w.r.t. bloc M_1 yields...

... the effect mediated via M_2, but not M_1



An imputation approach

(Tchetgen Tchetgen and Shpitser, 2012; Albert, 2012; VanderWeele and Vansteelandt, 2013)

To estimate

$$E\left\{Y(a, M_1(a'), M_2(a', M_1(a')))\right\}$$

- predict the outcome for each subject i
  as if (s)he had exposure a,
  adjusting for confounders C.
- average these predicted values in subjects with exposure a'

This does not require modelling the joint distribution of the mediators,

and is of special interest when the exposure is randomly assigned.

If not, additional propensity score weighting can be used.

Many ways of defining pathways

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- However, there are many more possible ways to 'define' a specific pathway.

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- When the exposure is continuous, there are infinitely many possible choices.

Many ways of defining pathways

- With a binary exposure and 2 mediators,
  there are 24 ways of decomposing
  the total effect into a direct effect and mediated effects.
  (Daniel et al., 2015)
- Some of these require stringent assumptions for identification.
- E.g. they set M_1 at $M_1(0)$ and M_2 at $M_2(0, M_1(1))$.

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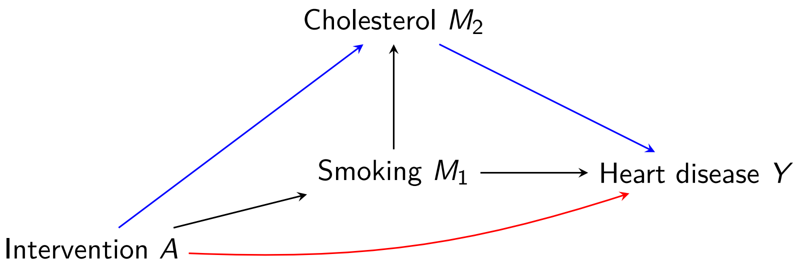
- VanderWeele and Vansteelandt (2013) focus on just 2 decompositions.
- We focus on the 6 decompositions that set M_1 at $M_1(a')$ and M_2 at $M_2(a'', M_1(a'))$.
  (Steen et al., 2016)
- This requires just slightly stronger assumptions.

Natural effect models enable parsimonious modelling

$$E\{Y(a, M_1(a'), M_2(a'', M_1(a')))\} = \beta_0 + \beta_1 a + \beta_2 a' + \beta_3 a''$$

(Lange, Vansteelandt and Bekaert, 2012; Vansteelandt, Lange and Bekaert, 2012; Steen et al., 2016)

- Natural effect models enable more parsimonious modelling
- β_1 captures the direct effect, not via M_1, M_2.
- β_2 captures the indirect effect via M_1.
- β_3 captures the indirect effect via M_2 but not M_1.



Natural effect models enable flexible modelling

(Lange, Vansteelandt and Bekaert, 2012; Vansteelandt, Lange and Bekaert, 2012; Steen et al., 2016)

- Is the indirect effect via cholesterol different depending on what level we control smoking?

$$E\left\{Y(a, M_1(a'), M_2(a'', M_1(a')))\right\} = \beta_0 + \beta_1 a + \beta_2 a' + \beta_3 a'' + \beta_4 a' a''$$

- Is the indirect effect via smoking (but not cholesterol) different for men and women?

$$\begin{aligned} E\left\{Y(a, M_1(a'), M_2(a'', M_1(a')))|C\right\} &= \beta_0 + \beta_1 a + \beta_2 a' + \beta_3 a'' \\ &\quad + \beta_4 a' C + \beta_5 C \end{aligned}$$

A weighted imputation approach

(Steen et al., 2016)

To estimate

$$E\left\{Y(a, M_1(a'), M_2(a'', M_1(a')))\right\}$$

- predict the outcome for each subject i
  as if (s)he had exposure a, adjusting for confounders C.
- calculate a weighted average of these predicted values
  in subjects with exposure a'', using weights

$$\frac{P(M_{1i}|A_i = a', C_i)}{P(M_{1i}|A_i = a'', C_i)}$$

If the exposure is not randomly assigned
additional propensity score weighting can be used.

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- calculate a weighted average of these predicted values
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$$\frac{P(M_{2i}|M_{1i}, A_i = a'', C_i)}{P(M_{2i}|M_{1i}, A_i = a', C_i)}$$

If the exposure is not randomly assigned
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Fitting natural effect models

- R package `medflex` enables fitting natural effect models with a single mediator.

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- Extensions to multiple mediators forthcoming, and currently available on request.

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- Extensions to multiple mediators forthcoming,
  and currently available on request.
- Weighting can be avoided
  so long as there are 2 mediators and no interactions.
- It can more generally be avoided
  using a sequential imputation approach.

Case study: WHO-LARES

- Data from 5882 adult respondents.

  (Shenassa et al., 2007)

$$
\begin{tikzcd}
 & \text{Physical illness } M_1 \arrow[dr] \arrow[dd] & \\
\text{Damp and moldy dwelling } X \arrow[ur] \arrow[rr] \arrow[dr] & & \text{Depression } Y \\
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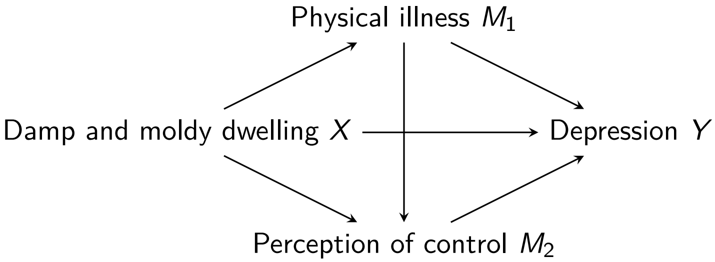

- A sense of compromised control over one's living environment

  (e.g. keeping a house clean in the face of recurrent mold)

  may mediate a potential link between
  residence in a damp and moldy dwelling and depression.

- To what extent?

Results from a main effects model

Table 1. Estimates and 95% Confidence Intervals of the Component Effects Odds Ratios.[a] WHO-LARES, 2002-2003.

	Weighted by $W_{1i,a'}$		Weighted by $W_{2i,a''}$	
Component	**Estimate**	**95% CI**	**Estimate**	**95% CI**
$\exp(\hat{E}_{A\to Y})$	1.260	1.000, 1.573	1.259	1.000, 1.571
$\exp(\hat{E}_{A\to M_1 Y})$	1.042	1.015, 1.069	1.041	0.995, 1.089
$\exp(\hat{E}_{A\to M_2\to Y})$	1.052	1.008, 1.098	1.048	1.016, 1.079

Abbreviations: CI, confidence interval; WHO-LARES, World Health Organization's Large Analysis and Review of European Housing and Health Status.
[a] Component effects as parameterized in the following natural effect model:
$\operatorname{logit} P\{Y(a, M_1(a'), M_2(a'', M_1(a'))) = 1 | C\} = \zeta_0 + \zeta_1 a + \zeta_2 a' + \zeta_3 a'' + \zeta_4^\top C.$

$$
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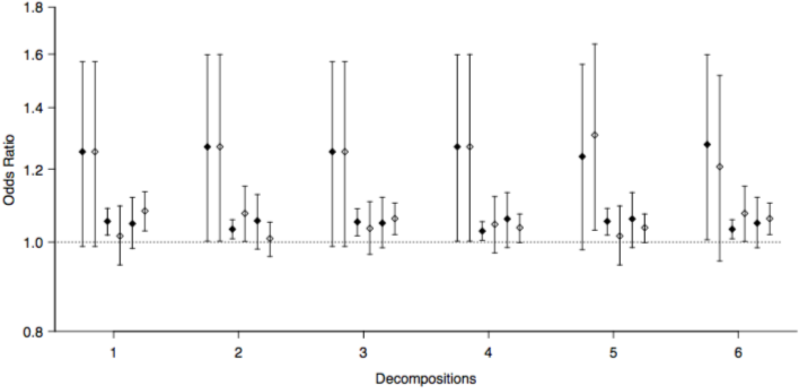
\end{tikzcd}
$$

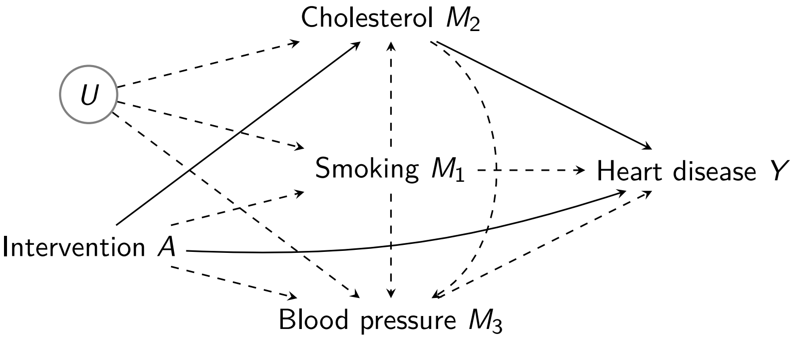
No evidence of interactions between pathways (P 0.49)



Summary: mediation analysis 'en bloc'

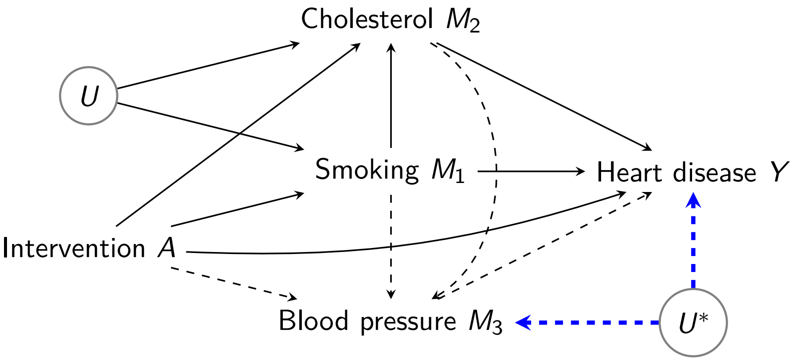
Considering multiple mediators 'en bloc' has some appeal, as it adjusts for confounding

- when mediators mutually influence each other;
- share unmeasured common causes.



Summary: mediation analysis 'en bloc'

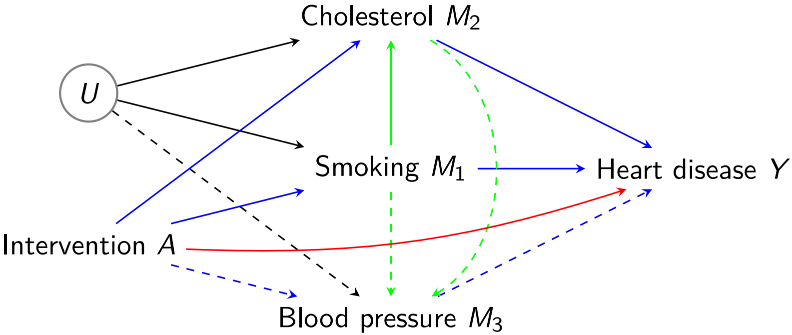
Larger blocs may thus seem preferable, although not necessarily...



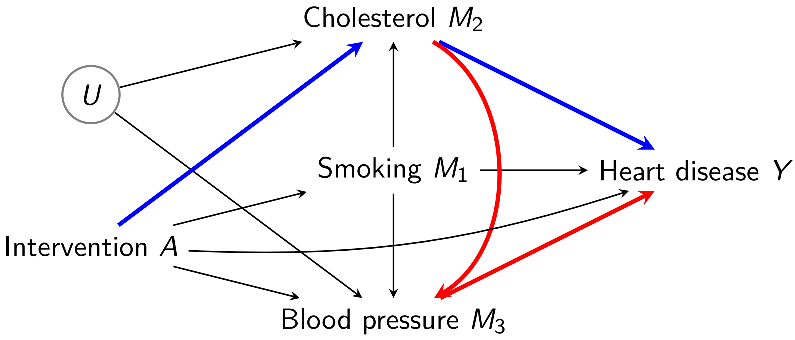
Summary: pathways

- Multiple mediation analysis 'en bloc' does not provide insight into separate pathways.
- Mediation analysis 'one at a time' can be problematic, and should be avoided.
- Sequential mediation analysis is preferred, but is also prone to bias when the mediators share unmeasured common causes.

Unmeasured confounding of the mediator associations

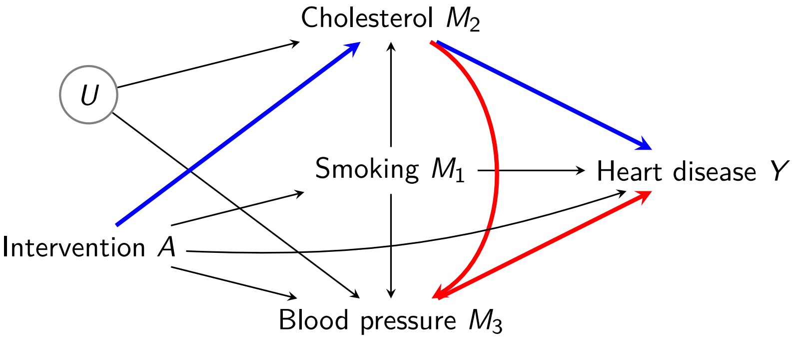


More refined mediation analysis



Sequential mediation analysis does not provide insight into all pathways,
but arguably it provides the most relevant ones.

Caveat: causal order of the mediators



- The causal order of the mediator is sometimes unknown.
- In recent work,
  we develop approaches for effect decomposition
  which give interpretable results regardless of causal ordering.

  (Vansteelandt and Daniel, 2017)

This presentation was based on ...

Daniel, R.M., De Stavola, B.L., Cousens, S.N. and Vansteelandt, S. (2014). Causal mediation analysis with multiple mediators. *Biometrics.*

Lange, T., Vansteelandt, S. and Bekaert, M. (2012). A simple unified approach for estimating natural direct and indirect effects. *American Journal of Epidemiology*, 176, 190-195.

Steen, J., Loeys, T., Moerkerke, B. and Vansteelandt, S. (2015) Medflex: An R Package for Flexible Mediation Analysis Using Natural Effect Models. *Journal of Statistical Software*, in press.

Steen, J., Loeys, T., Moerkerke, B. and Vansteelandt, S. (2016). Flexible mediation analysis with multiple mediators. *American Journal of Epidemiology*, in press.

VanderWeele, T. and Vansteelandt, S. (2013). Mediation Analysis with Multiple Mediators. *Epidemiologic Methods*, **2**, 95-115.

Vansteelandt, S. and Daniel, R.M. (2017). Interventional effects for mediation analysis with multiple mediators. *Epidemiology*, in press.

Sum individual mediated effects $\neq$ joint mediated effect

Joint mediated effect:

$$Y(1, M_1(1), M_2(1)) - Y(1, M_1(0), M_2(0))$$

Sum individual mediated effects $\neq$ joint mediated effect

Joint mediated effect:

$$Y(1, M_1(1), M_2(1)) - Y(1, M_1(0), M_2(0))$$

Sum of the individual mediated effects:

$$Y(1, M_1(1)) - Y(1, M_1(0)) + Y(1, M_2(1)) - Y(1, M_2(0))$$

Sum individual mediated effects $\neq$ joint mediated effect

Joint mediated effect:

$$Y(1, M_1(1), M_2(1)) - Y(1, M_1(0), M_2(0))$$

Sum of the individual mediated effects:

$$\begin{aligned} &Y(1, M_1(1)) - Y(1, M_1(0)) + Y(1, M_2(1)) - Y(1, M_2(0)) \\ &= Y(1, M_1(1), M_2(1)) - Y(1, M_1(0), M_2(1)) \end{aligned}$$

Sum individual mediated effects $\neq$ joint mediated effect

Joint mediated effect:

$$Y(1, M_1(1), M_2(1)) - Y(1, M_1(0), M_2(0))$$

Sum of the individual mediated effects:

$$\begin{aligned} & Y(1, M_1(1)) - Y(1, M_1(0)) + Y(1, M_2(1)) - Y(1, M_2(0)) \\ & = Y(1, M_1(1), M_2(1)) - Y(1, M_1(0), M_2(1)) \\ & \qquad + Y(1, M_1(1), M_2(1)) - Y(1, M_1(1), M_2(0)) \end{aligned}$$

Sum individual mediated effects $\neq$ joint mediated effect

Joint mediated effect:

$$Y(1, M_1(1), M_2(1)) - Y(1, M_1(0), M_2(0))$$

Sum of the individual mediated effects:

$$\begin{aligned} & Y(1, M_1(1)) - Y(1, M_1(0)) + Y(1, M_2(1)) - Y(1, M_2(0)) \\ = {} & Y(1, M_1(1), M_2(1)) - Y(1, M_1(0), M_2(1)) \\ & \quad + Y(1, M_1(1), M_2(1)) - Y(1, M_1(1), M_2(0)) \end{aligned}$$

The difference

$$\begin{aligned} & Y(1, M_1(1), M_2(1)) + Y(1, M_1(0), M_2(0)) \\ & - Y(1, M_1(0), M_2(1)) - Y(1, M_1(1), M_2(0)) \end{aligned}$$

is a type of mediated interaction, which may be non-zero when both mediators interact at the individual level.