PATHWAYS

Current Methods in Mediation Analysis

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IEU Symposium on Statistical Methods for Epigenetic Change
Bristol, 6 June 2014

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THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

National Centre for Research Methods

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Mediation

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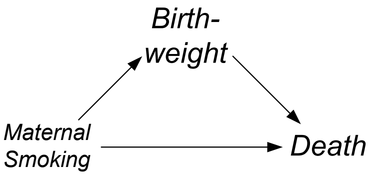
- In other words we are interested in the study of mediation.

Example I

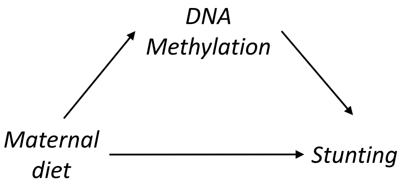
Maternal smoking, birth weight, and infant mortality



For example, how much of the effect of maternal smoking on infant mortality is due to its effect on birth weight?

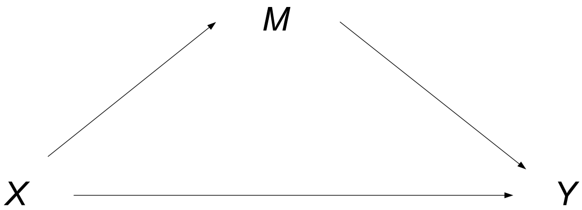
Example II

Maternal nutrition at conception, methylation and stunting



Study of Gambian infants (Dominiguez-Salas *et al.*, *Nature Comm*, 2014)

Typical setting



- Write X for the exposure, M for the mediator and Y for the outcome.

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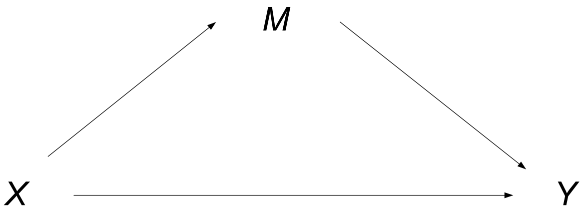

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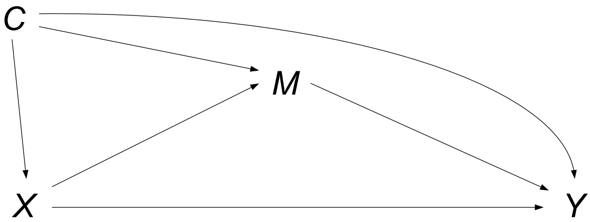

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- Let M and Y be continuous.
- Let's explicitly include confounders C.

Outline

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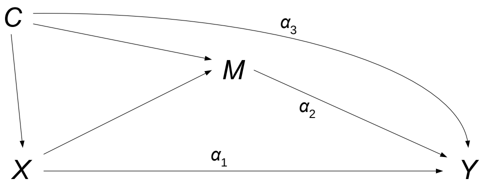
Combination of simple least squares regressions



Consider two regression models:

$$E(Y|C,X,M) = \alpha_0 + \alpha_1 X + \alpha_2 M + \alpha_3^T C$$
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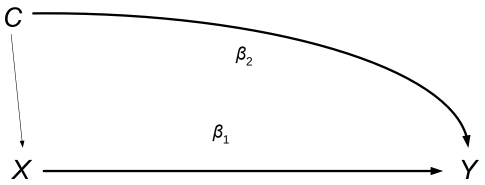

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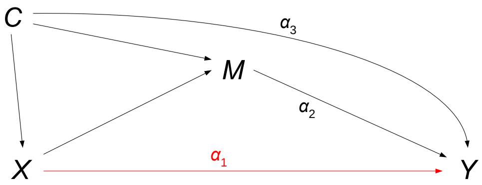

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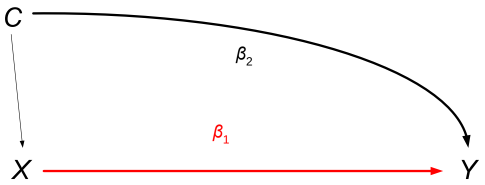

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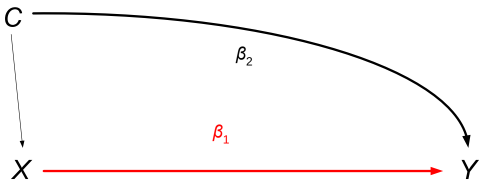

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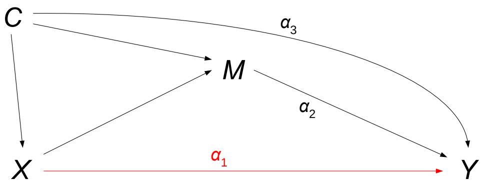

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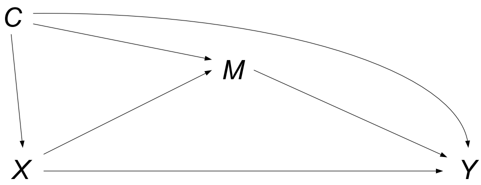

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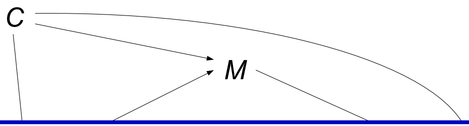

- Estimation via ordinary least squares.
- Various options (delta method, bootstrapping) to obtain SE for the indirect effect.

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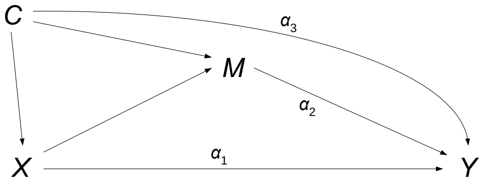
Outline

A linear Structural Equation Model

Wright, 1921



Alternatively, consider a (linear) structural equations model:

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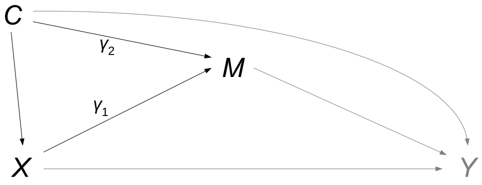

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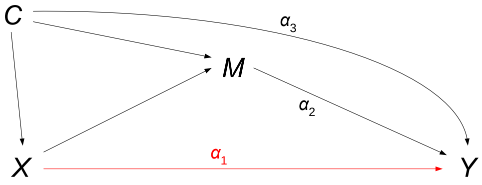

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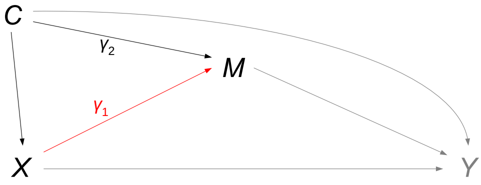

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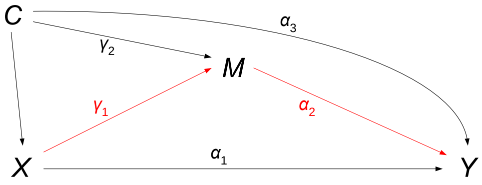

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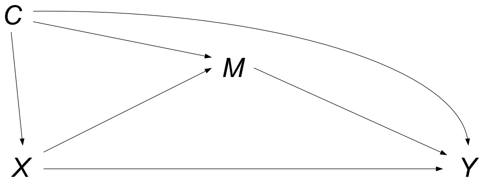

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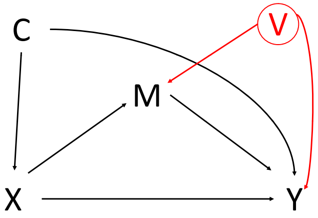

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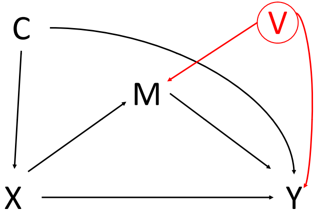

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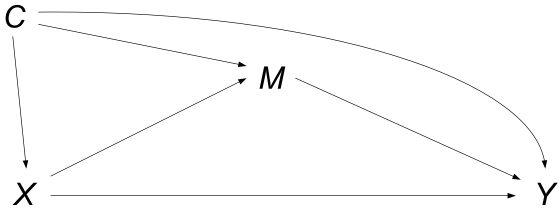
Problem 3: intermediate confounding



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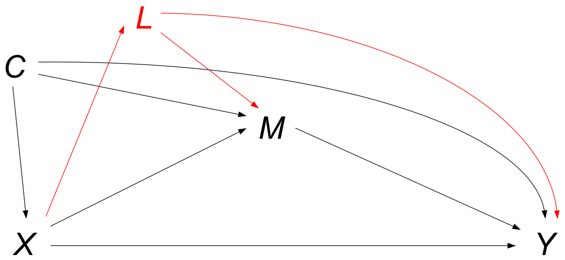

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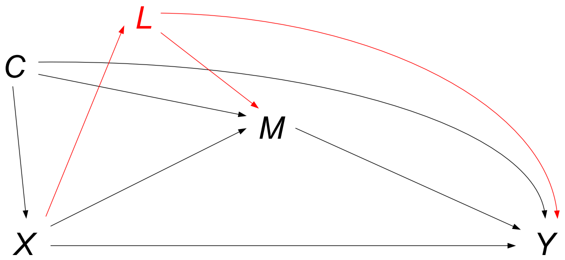

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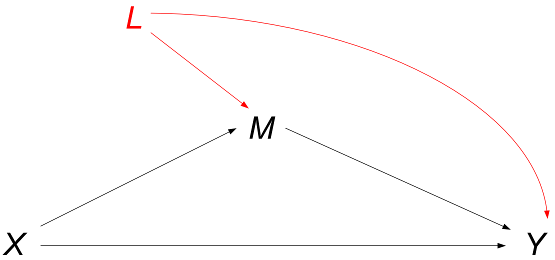

- Such L are problematic.
- Let us ignore C for simplicity, and, let us even ignore the arrow from X to L at first, ie L is NOT an intermediate confounder in this diagram for now…

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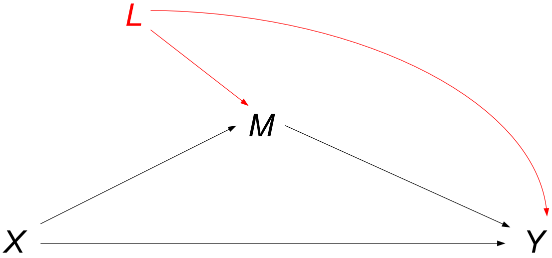

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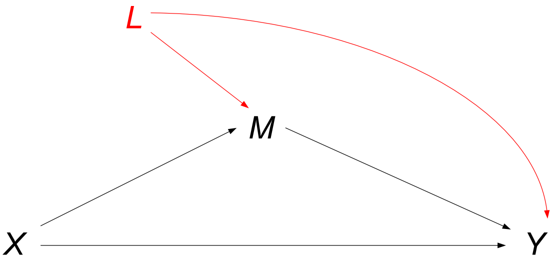

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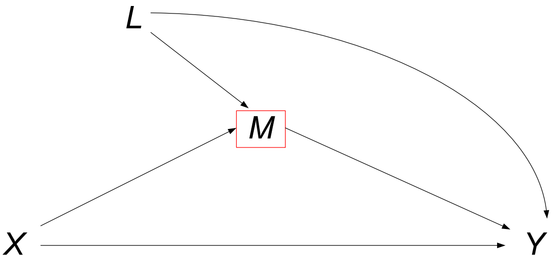

- L is a confounder for the M-Y relation and therefore cannot be ignored.
- However conditioning on M (in the model for Y) induces an association between X and L even if there was none there before (and would alter an existing association).
- Hence we should also condition on L . . .

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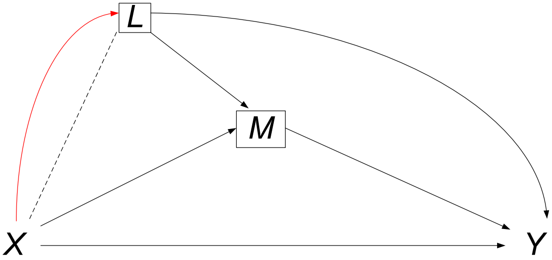

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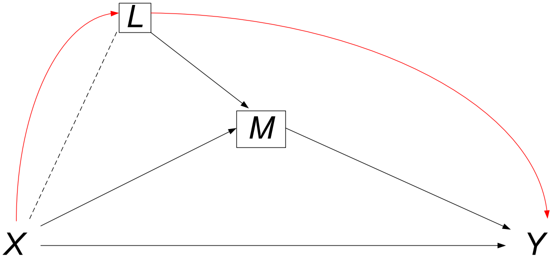

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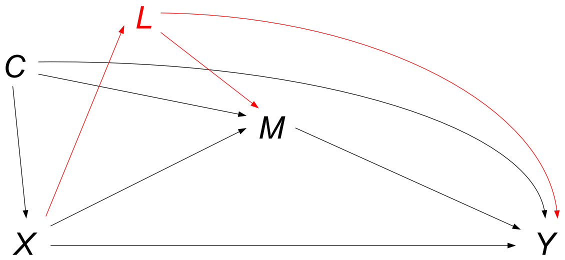

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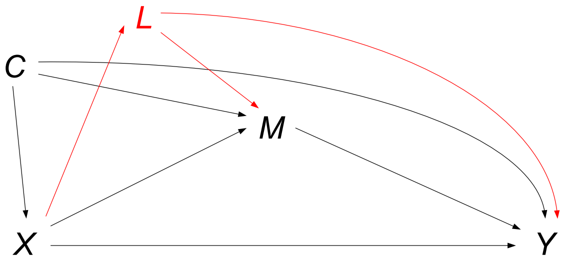

- But this is NOT a solution when *L* is affected by *X*.
- Since we block part of the direct effect (unmediated by *M*).
- Thus standard regression cannot be used when there is intermediate confounding.
- (SEMs could deal with this, but only for linear models for *L*, *M* and *Y* ...).

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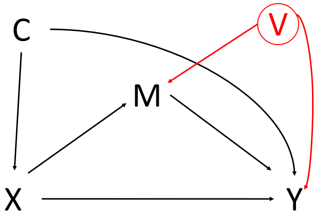

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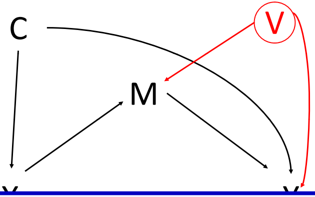

More recent contributions from the causal inference literature have brought clarity to these issues, and greater flexibility to the modelling.

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These counterfactuals are central to the (model-free) definitions of direct/indirect effects in causal inference.

Total causal effect

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- Note that this can also be written as

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

Controlled direct effect

Pearl, 2001

- The controlled direct effect of X on Y when M is controlled at m, expressed as a mean difference is

$$\text{CDE}(m) = E\{Y(1, m)\} - E\{Y(0, m)\}.$$

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- This (as always with a causal contrast) is a comparison of two hypothetical worlds.
- In the first, X is set to 1, and in the second X is set to 0. In both worlds, M is set to m.
- By keeping M fixed at m, we are getting at the direct effect of X, unmediated by M.

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- But this turns out not to be possible using this definition of a controlled direct effect.
- For this reason, it is useful to have a different definition of a direct effect.

Natural direct effect

Pearl, 2001; Robins and Greenland, 1992

- The natural direct effect of X on Y expressed as a mean difference is

$$\text{NDE} = E\left[Y\{1, M(0)\}\right] - E\left[Y\{0, M(0)\}\right].$$

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$$\text{NDE} = E\left[Y\left\{1, M\left(0\right)\right\}\right] - E\left[Y\left\{0, M\left(0\right)\right\}\right].$$

- This is a comparison of two hypothetical worlds.
- In the first, X is set to 1, and in the second X is set to 0. In both worlds, M is set to $M(0)$, the value it would take if X were set to 0.
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- If no individual-level interaction between X and M, $\text{CDE}(m) = \text{NDE} \;\; \forall m$.

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- In the first, M is set to $M(1)$ and in the second M is set to $M(0)$. In both worlds, X is set to 1.
- X is allowed to influence Y only through its influence on M. Thus it is an indirect effect through M.

Effect decomposition

Now we see that the sum of the natural direct and indirect effects is

$$\begin{aligned} \text{NDE} + \text{NIE} = & \; E\left[Y\left\{1, M(0)\right\}\right] - E\left[Y\left\{0, M(0)\right\}\right] \\ & + E\left[Y\left\{1, M(1)\right\}\right] - E\left[Y\left\{1, M(0)\right\}\right] \\ & = E\left[Y\left\{1, M(1)\right\}\right] - E\left[Y\left\{0, M(0)\right\}\right] = \text{TCE}, \end{aligned}$$

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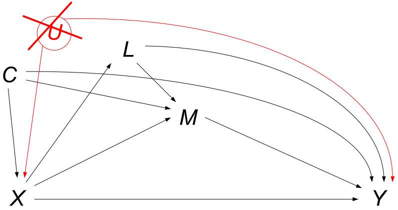
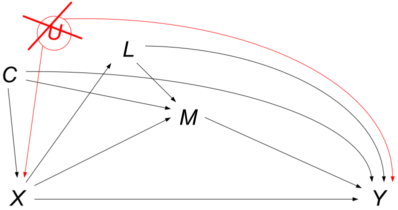
- As well as technical assumptions of no interference and consistency, there are no unmeasured confounding assumptions, and more...

Assumptions for identification: TCE



- No unmeasured confounding of the X–Y relationship.

Assumptions for identification: CDE



- No unmeasured confounding of the X–Y or M–Y relationships.

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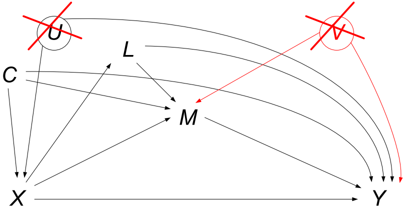

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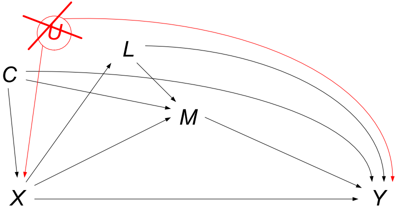

- No unmeasured confounding of the X–Y, M–Y, or X–M relationships.

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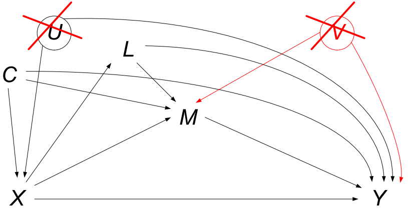

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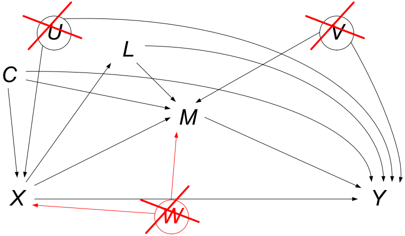

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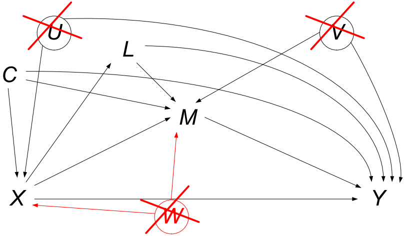

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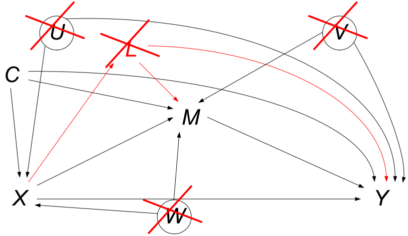

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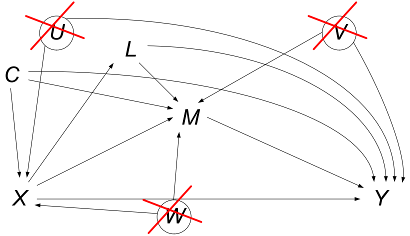

- No unmeasured confounding of the X–Y, M–Y, or X–M relationships.
- AND, in addition, either:
  - No intermediate confounding, or
  - Some restriction on the extent to which X and M interact in their effect on Y (Petersen et al, 2006).

Outline

G-computation formula for the CDE
Robins 1986

- Let's look at how the CDE is estimated:

$$\mathrm{CDE}(m) = E\{Y(1,m)\} - E\{Y(0,m)\}$$
$$= \int E(Y|C=c, X=1, L=l, M=m)\, f_{L|C,X}(l|c,1)\, f_C(c) dl\, dc$$
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- Both models can be completely flexible: they can include non-linearities and interactions.
- By marginalising over $L|C,X$, intermediate confounding is appropriately dealt with.

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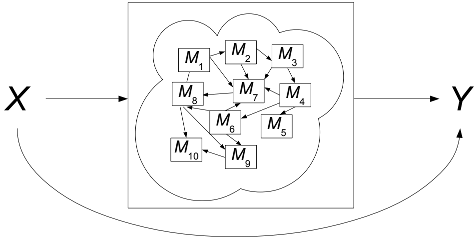
  - other flavours of g-estimation (Joffe and Greene, 2009; Vansteelandt, 2009).

Outline

Multiple mediators



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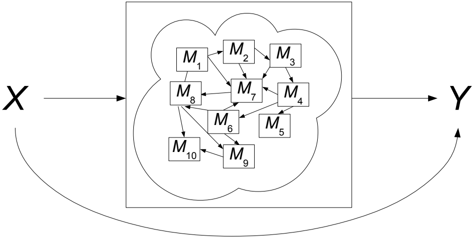
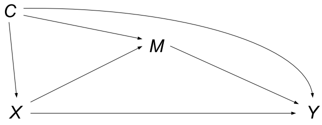


- Often there are many mediators of interest, eg many metabolites potentially mediating the relationship between CVD SNPs and CVD.
- Unless these do not causally affect one another (unlikely), and if we are interested in path-specific effects, this makes things much more complicated (Daniel et al, under review).

Interactions



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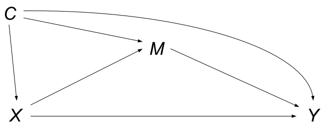

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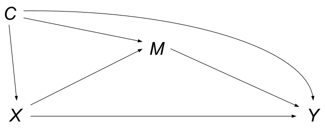

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- Standard approaches (regression of Y on X, M, $X * M$ and confounders) are then essentially attempting to estimate the CDE at each m and assess whether these CDEs are all the same.
- But if there are unmeasured confounding of M and Y, for example, this would lead to bias in these estimates and, potentially, to misleading conclusions about the presence and magnitude of any interaction.

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Quick summary

- Traditional approaches are somewhat limited, and too vague for these limitations to be always apparent.

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- But these (and more) were needed in the traditional approach even if we didn't realise it.
- Hygienic thinking keeps us honest, and aids sensitivity analyses. . .

Outline

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