PATHWAYS

Mediation analysis for life course epidemiology

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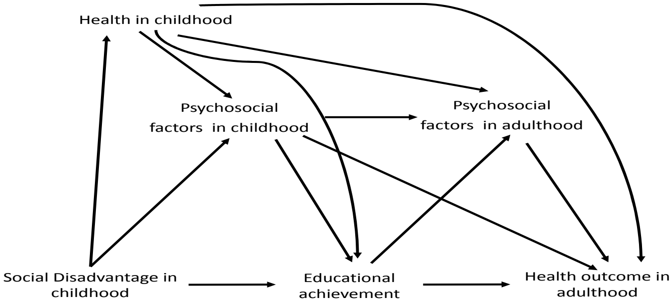
THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

NCRM National Centre for Research Methods

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Mediation

In life course studies we focus on distal exposures (*e.g.* social disadvantage) for later life outcomes:



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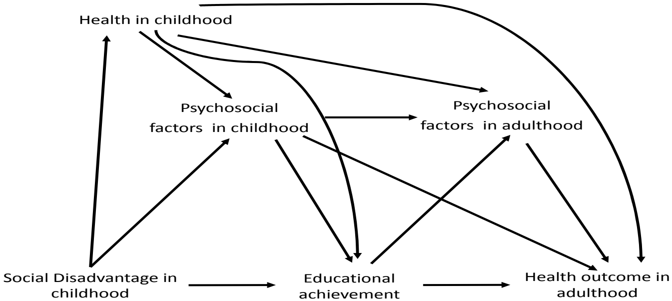
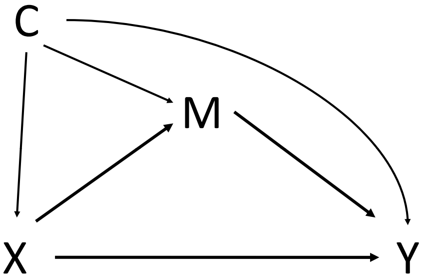


Interest: disentangle the underlying processes.

Keeping it simple

Exposure X, mediator M, outcome Y and confounders C.



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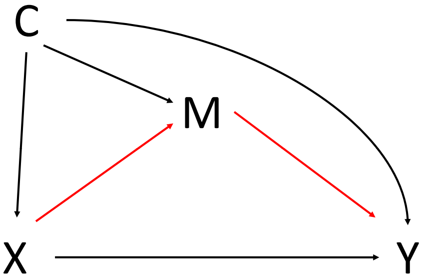

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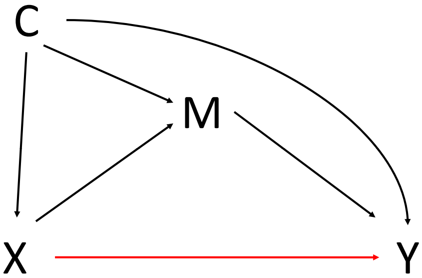
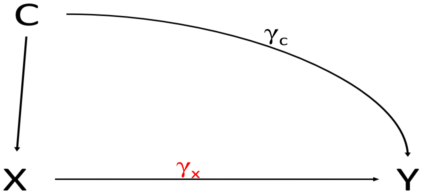


Outline

1. Standard approach
2. A more general approach
3. Example: ED in adolescent girls
4. Summary

Standard approach to mediation analysis

For Y a continuous outcome, *e.g.* birth weight:



- Regress Y on the exposure X and confounding factors C:

$$E(Y|X,C) = \gamma_0 + \gamma_x X + \gamma_c C$$

γ_x this is interpreted as the total effect.

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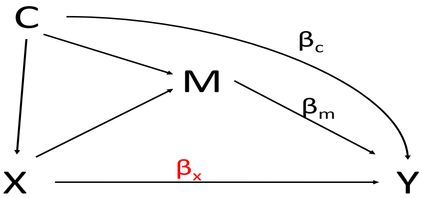

- Adding the mediator M and expanding the model for Y:

$$E\left(Y|X, M, C\right) = \beta_0 + \beta_x X + \beta_m M + \beta_c C$$

β_x is interpreted as the direct effect.

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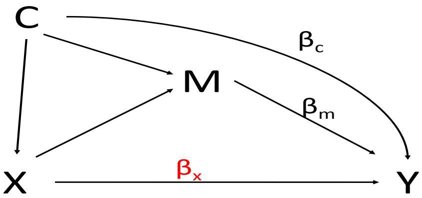

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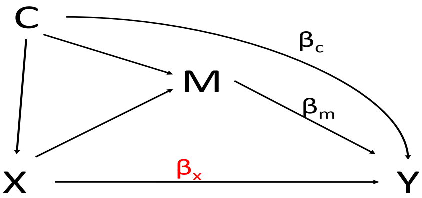

- The difference between total and direct effect, $\delta_x = \gamma_x - \beta_x$, is interpreted as the indirect effect.
- This can also be derived using the multiplication of effects method (as defined in SEMs).

Four limitations of the standard approach

1. If the model were:

$$E\left(Y|X,M,C\right) = \beta_0 + \beta_x X + \beta_m M + \beta_{xm} XM + \beta_c C$$

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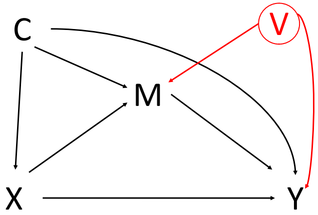
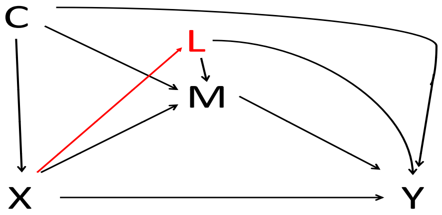
3. It is not generally recognized that if there may be unaccounted confounders V of the M–Y relationship:



Four limitations of the standard approach (cont'd)

4. If a measured confounder is like L, *i.e.* a variable that is a consequence of X (*i.e.* intermediate confounder):



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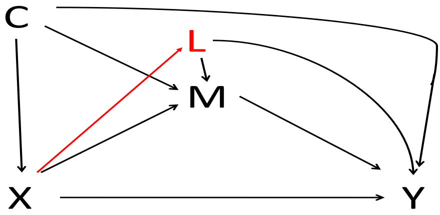

$$E(Y|X, M, C) \quad = \quad \beta_0 + \beta_x X + \beta_m M + \beta_c C + \beta_l L$$

β_x would not measure the direct effect of X:
the effect of X that is not mediated by M (the direct effect) includes $X \to L \to Y$, but controlling for L removes it!

A more general approach to mediation analysis

The causal inference framework

- The causal inference literature on mediation provides general definitions of direct and indirect effects that:
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Potential outcomes

- $Y(x)$: the potential values of Y that would have occurred had X been set, possibly counter to fact, to the value x.
- $M(x)$: the potential values of M that would have occurred had X been set, possibly counter to fact, to the value x.
- $Y(x, m)$: the potential values of Y that would have occurred had X been set, possibly counter to fact, to the value x and M to m.

Total Causal Effect (TCE): definition

The average total causal effect of X, comparing exposure level $X = 1$ to $X = 0$, can be defined as the linear contrast:

$$TCE = E[Y(1)] - E[Y(0)]$$

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.

We are working throughout on the mean difference scale... alternatives exist.

Mediation parameters in causal inference

(a) The Controlled direct effect (CDE(m)):

$$CDE(m) \;=\; E\left[Y\left(1, m\right)\right] - E\left[Y\left(0, m\right)\right]$$

It 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, CDE(m) is the direct effect of X, unmediated by M (in general it varies with m).

Mediation parameters in causal inference (cont'd)

(b) The Natural Direct Effect (NDE):

$$NDE = E[Y(1, M(0))] - E[Y(0, M(0))]$$

It 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 the natural value $M(0)$, *i.e.* the value it would take if X were set to 0.
- Since M is the same (*within* individual) in both worlds, we are still getting at the direct effect of X, unmediated by M.

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(c) The Natural Indirect Effect (NIE):

$$NIE = TCE - NDE$$

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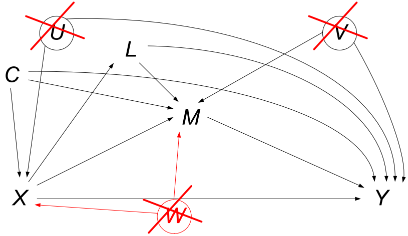
Will focus on these natural effects

Assumptions for estimation of natural effects



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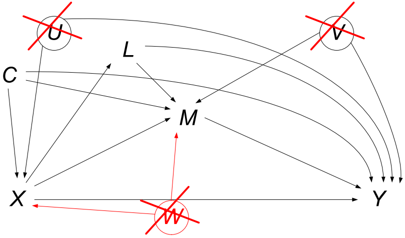

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    - no intermediate confounding,
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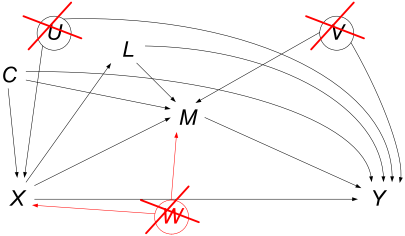
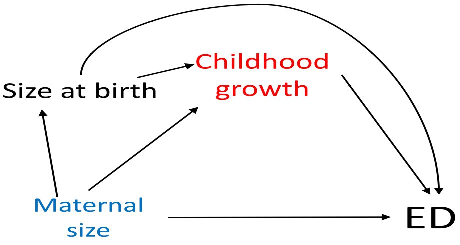


- In addition, either:
  - no intermediate confounding,
  - or some model restrictions.
- Estimation: choice of fully parametric or semi-parametric approaches.

Eating disorders (ED) in adolescent girls

- ED comprise a variety of heterogeneous diseases
- Maternal body size is a possible risk factor
- Childhood growth may act as mediator (with size at birth an intermediate confounder).



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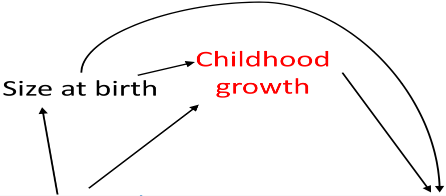

What effect does intervening on maternal BMI have on the child's ED symptoms in a world where maternal BMI has no effect on her child growth trajectory?

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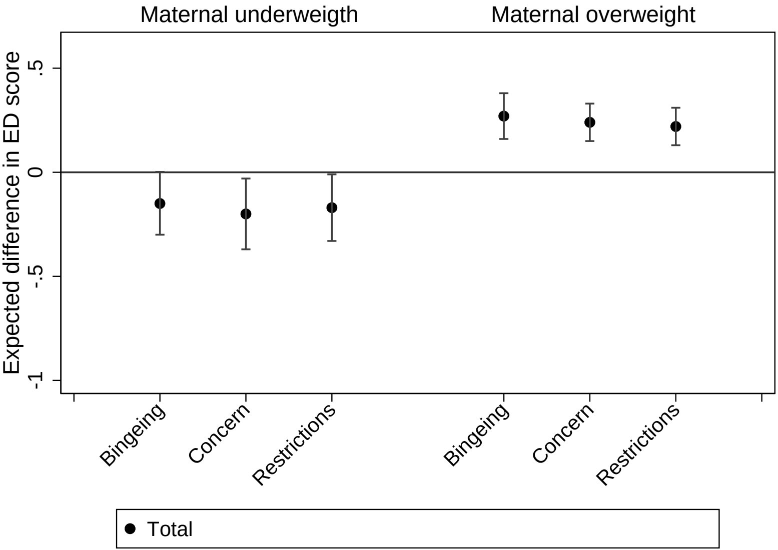
- Background confounders: pre-pregnancy maternal psychopathology, maternal age, education, social class.
- Assumptions: No unmeasured confounding of the X–Y, X–M, M–Y relations; no X–M interactions.
- Estimation: Fully-parametric via Monte Carlo simulation (with imputation and bootstrapped SEs).

Results

N=3,526



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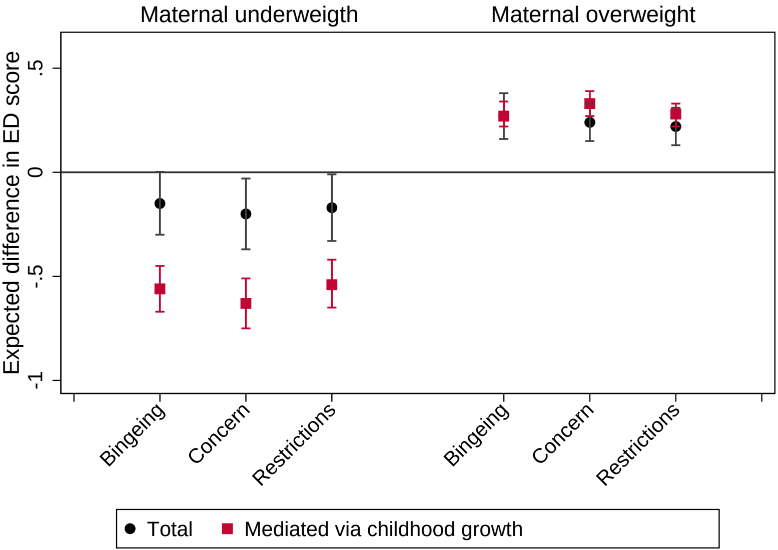

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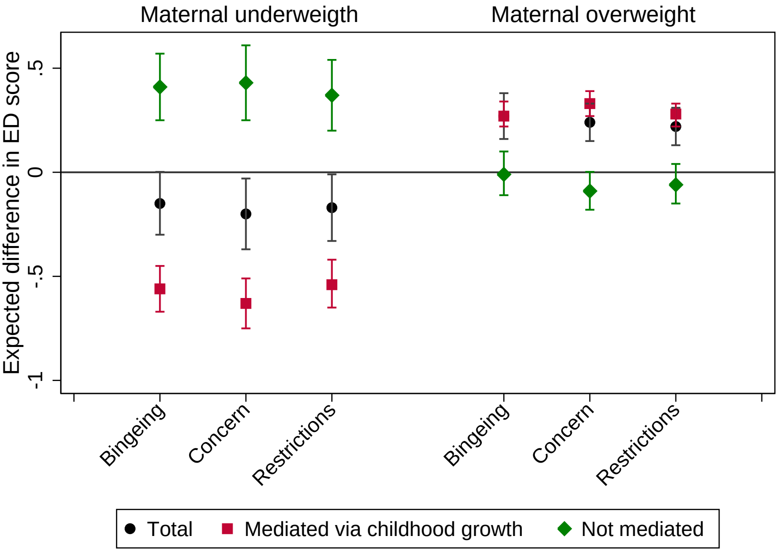

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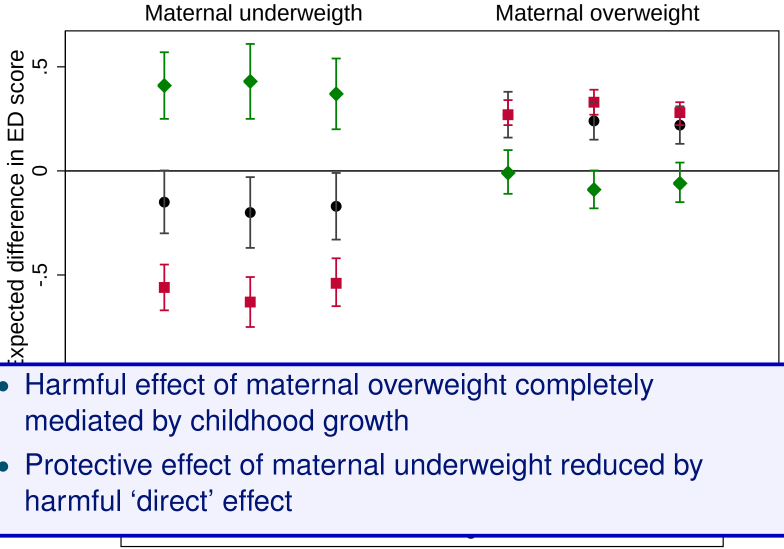

- Harmful effect of maternal overweight completely mediated by childhood growth
- Protective effect of maternal underweight reduced by harmful ‘direct’ effect

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Thank you!

References

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