Multiple Questions for Multiple Mediators

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Mediation-type enquiries

Increasingly, mediation-type questions are posed in several contexts:

- RCTs:

  Is cognitive behaviorial therapy (CBT) acting via increased compliance to medication in reducing suicide rates?

- Public health interventions:

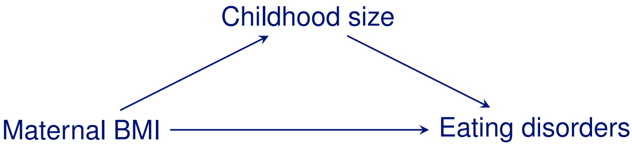
  Does an enhanced school environment improve students' physical activity via their empowerment?

- Aetiological studies:

  What proportion of the effect of prenatal factors on eating disorders can be explained by childhood growth?

Mediation

These questions involve studying the extent to which the effect of one variable on another is mediated by some intermediate variable(s).
For example,



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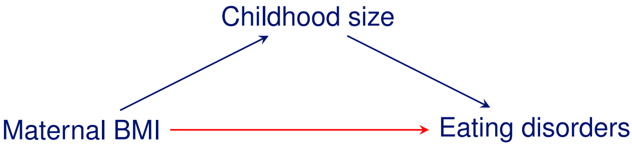

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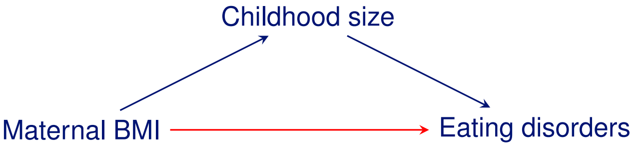

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Talk is about the complexities of attempting mediation analysis

Outline

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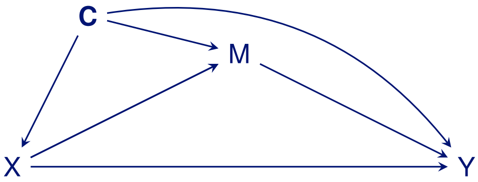
A long tradition

- Mediation analysis is not new; statisticians have been attempting it using traditional regression models for nearly a century
- It is inspired by path analysis (Wright, 1921, 1934)
- It is popular in the social sciences, while in epidemiology a less structured approach is often adopted
- In each of these approaches a set of regression models is specified

Path analysis for a simple setting

- Consider a structure with exposure X, continuous mediator M, continuous outcome Y and confounders $\mathbf{C}$
- Path analysis would define two regression models:



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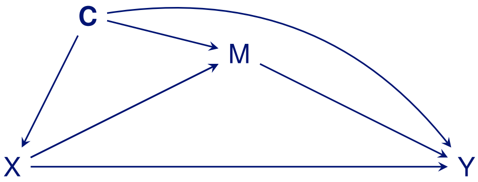

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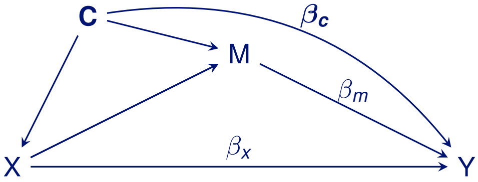

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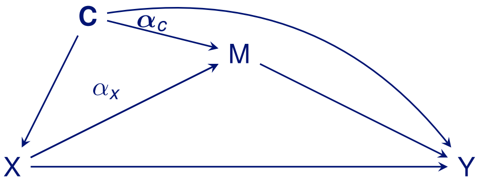

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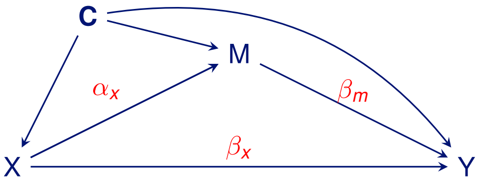

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Interpretation: — β_x as the direct effect of X on Y

—$\alpha_x \beta_m$ as the indirect effect of X on Y (*path tracing rule*)

Problems

1. Informal definitions

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- Path tracing rules are derived from partitioning of correlations (Wright, 1934): not based on a formal causal argument
- Yet, mediation enquiries make sense only if we think of them as causal questions:
  - When we say M mediates the effect of X on Y, we mean that X has a causal effect on Y and that some of this effect is explained by the fact that X has a causal effect on M which in turn has a causal effect on Y.

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2. Reliance on linearity

- If the model for Y were specified as:

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- If Y were a binary variable modelled by logistic regression, even in the absence of an X–M interaction, application of the path tracing rule would not be sensible.

Problems

3. M–Y confounding

It is not always sufficiently emphasised that common causes of M and Y should be controlled for. Consider this simple diagram:

$$
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D \arrow[r] \arrow[rr, bend left] & M \arrow[dr] & \\
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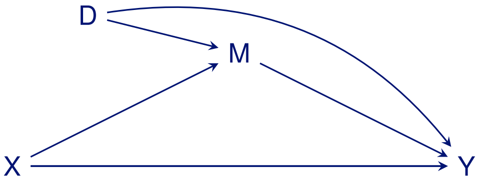

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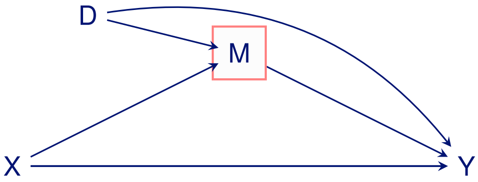

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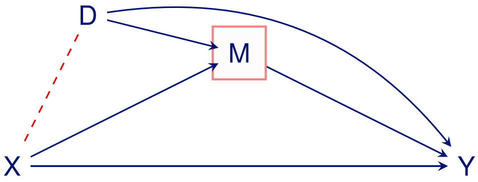

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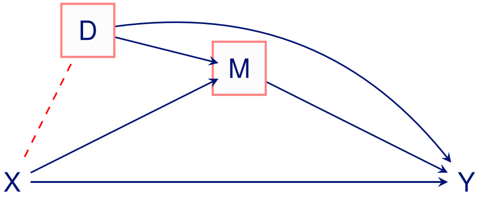

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- Conditioning on D too, as in:

$$E(Y) = \beta_0^* + \beta_x^* X + \beta_m^* M + \beta_d^* D$$

renders both paths blocked, so that β_x^* represents the direct effect.

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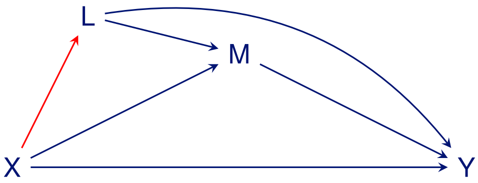
Complications arise with intermediate confounders such as L: these are common causes of M and Y that are affected by X.



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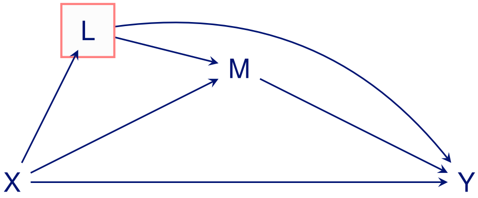

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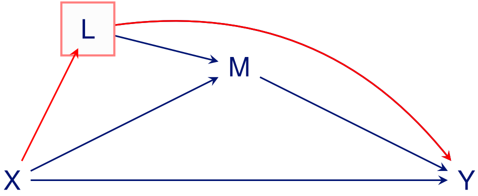

- We have just seen that common causes of M and Y should be controlled for
- However this would block part of the direct effect from X to Y (via L but not via M)

Outline

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Contributions from the causal inference literature have both formalised and generalised classical mediation methods, addressing some of these problems

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- It leads to defining *potential* (counterfactual) *outcomes* and *mediators*
- These counterfactuals are central to the definitions of direct/indirect effects in this framework

Counterfactuals

- $Y(x)$
  the value that Y would take if we intervened on X and set it (possibly counter to fact) to the value x.

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  $Y\{x, M(x^*)\}$
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Mediation effects (estimands) are defined in terms of these potential entities, without invoking any parametric model

Natural direct effect

Pearl, 2001; Robins and Greenland, 1992

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- 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.
- Since M is the same (*within* subject) in both worlds, we are still getting at the direct effect of X.

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The direct and indirect effects together sum to the total causal effect:

TCE=NDE+NIE

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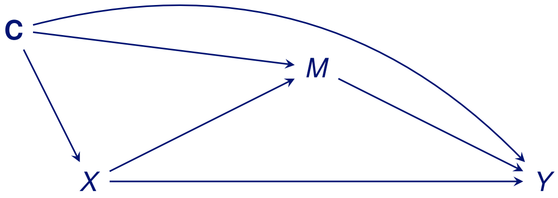

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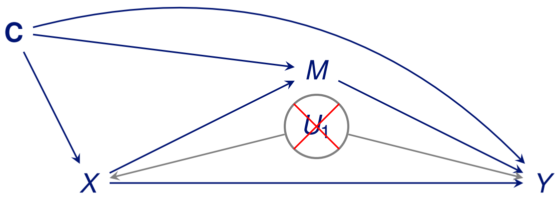

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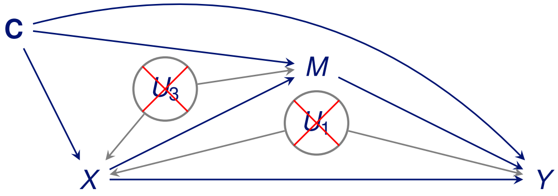

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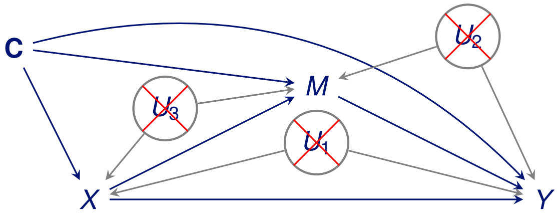

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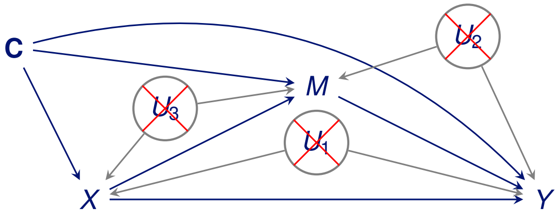

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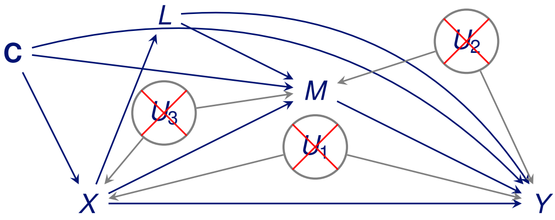

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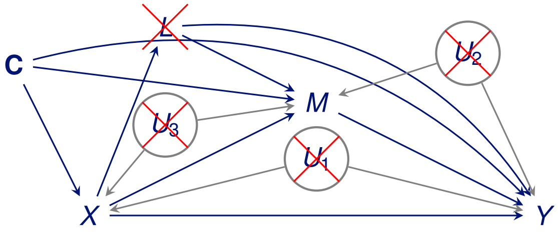

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- No need for the cross-world assumption for their identification; however, their sum is not TCE

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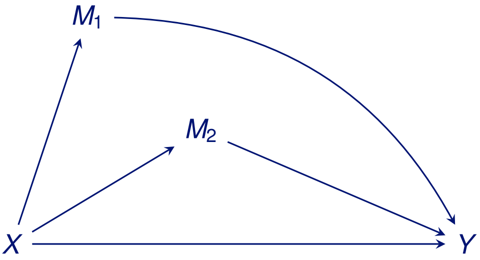

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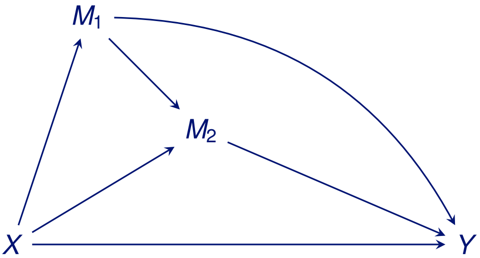

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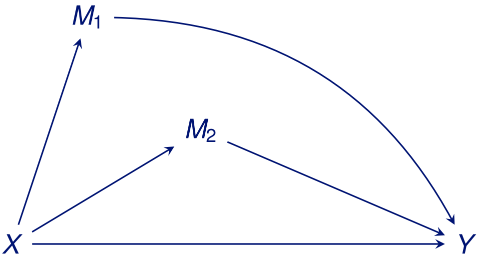

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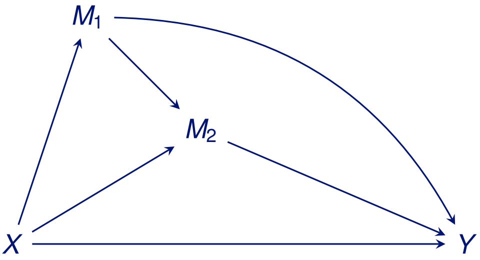

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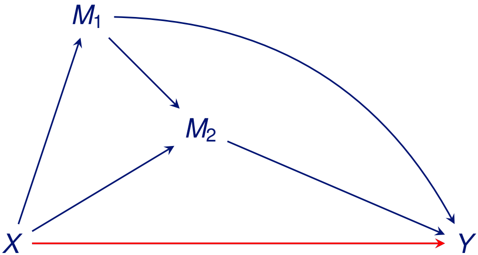
4. If the mediators are repeated measures of the same dimension, focus on interventional effects of time-varying mediators [Lin *et al.* 2016, VanderWeele & Tchetgen-Tchetgen 2017]

1. & 2. Multivariable and sequential mediation

(a) Estimate natural effects for M_1 and M_2 jointly; save $\widehat{\mathrm{NDE}}$



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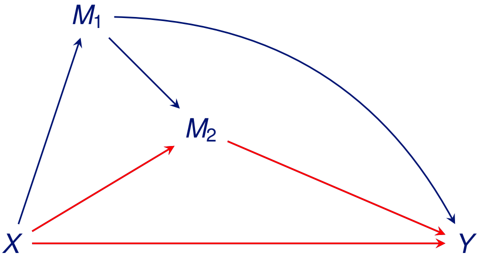

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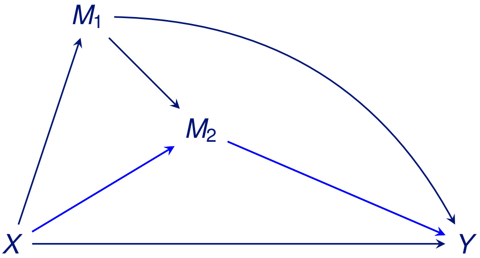

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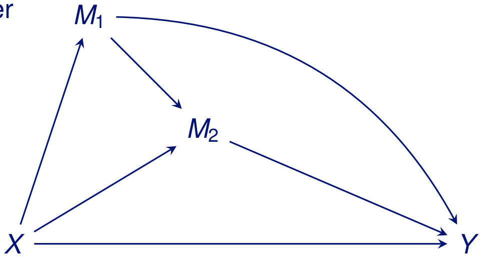
These steps lead to partition of TCE into 3 components:

- via M_1 and downstream
- via M_2 only
- via neither



3. Interventional effects for MM

- Vansteelandt and Daniel generalized interventional effects to the multiple mediators setting [Vansteelandt and Daniel, 2016]:

$$\text{RIA-NDE}_1 = E\left\{\sum_{m_1}\sum_{m_2} E\left(Y\left(x, m_1, m_2|c\right)\right)\left\{P\left(M_1(x) = m_1|c\right) - P\left(M_1(x^*) = m_1|c\right)\right\} P\left(M_2(x) = m_2|c\right)\right\}$$

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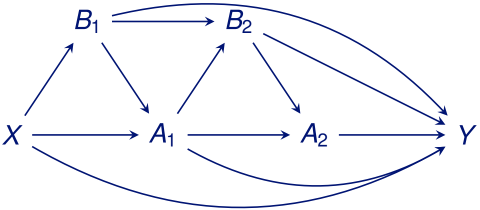
- Similar definitions for RIA-NDE and RIA-NIE$_2$
- They do not require an ordering of the mediators
- Identification does not require assumption of no omitted confounders for the mediators
- Interpretation:
  - RIA-NDE$_1$: effect of X on Y via M_1 but not its descendants
  - RIA-NDE$_2$: effect of X on Y via M_2 but not its descendants
  - Remainder in the decomposition of TCE, RIA-NIE$_{12}$, captures the indirect effect of X on the dependence among the mediators

4. Interventional effects for time-varying mediators

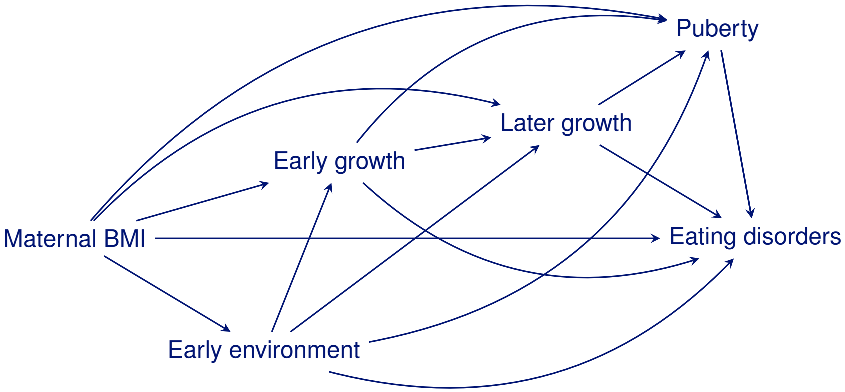
- Similar extensions of the definition of RIA natural effects given by VanderWeele & Tchetgen-Tchetgen (2017) for the setting with time-varying exposures, mediators, and confounders.
- A simple example with time-varying mediator A and time-varying confounder B:



Outline

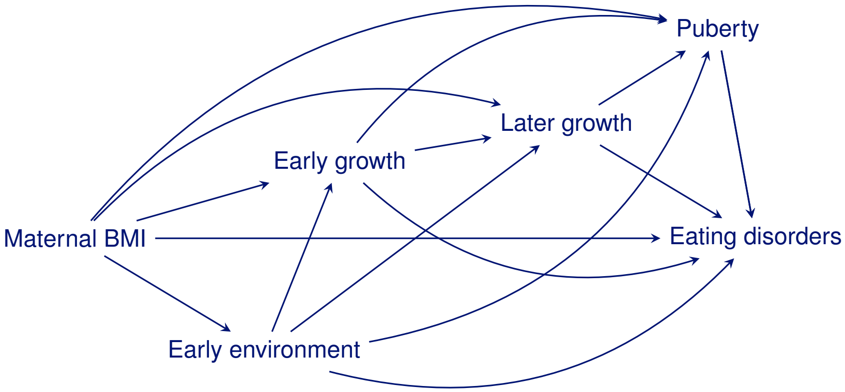
Eating disorders (ED) in adolescent girls

- ED are heterogeneous psychiatric illnesses with typical onset in adolescence
- Evidence of intergenerational dependencies: maternal BMI
- Explanations: environmental factors, childhood metabolic and growth factors



Eating disorders (ED) in adolescent girls

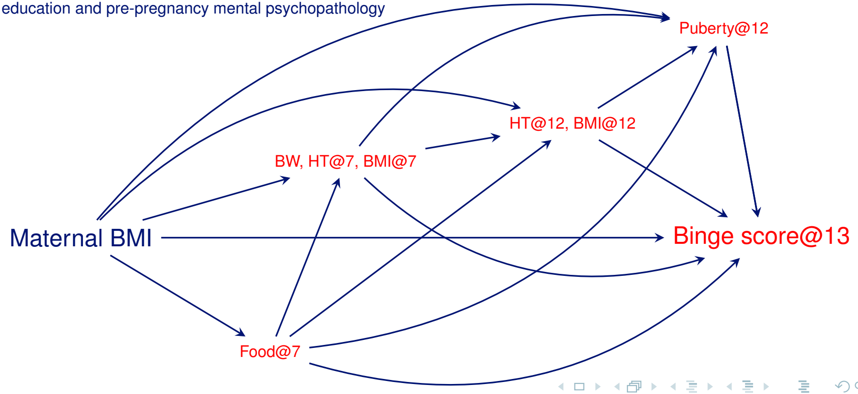
Q1. Do all mediators combined lead to a null direct effect?
Q2. Are early factors more important than late factors?
Q3. Which aspect of growth?



The ALSPAC Study

Cohort of children born in 1991-92 in SW England (3500 girls)

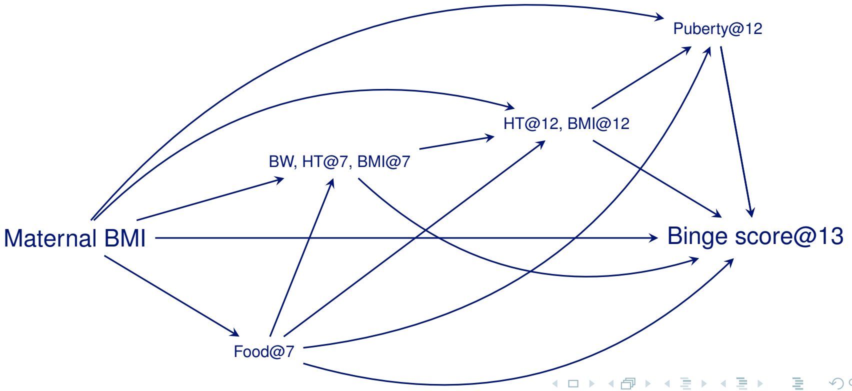
- Outcome: *"Binge/overeating"* score, from parental reports @13.5y
- Exposure: Pre-pregnancy maternal BMI: BMI$<$25kg/m^2 *vs.* BMI$>$25 kg/m^2
- Mediators: Birth weight, height and BMI measures, attitude to food, breast development
- Confounders: maternal age, social class, education and pre-pregnancy mental psychopathology



1. Natural effects for the 8 mediators jointly

Do all mediators combined lead to a null direct effect?

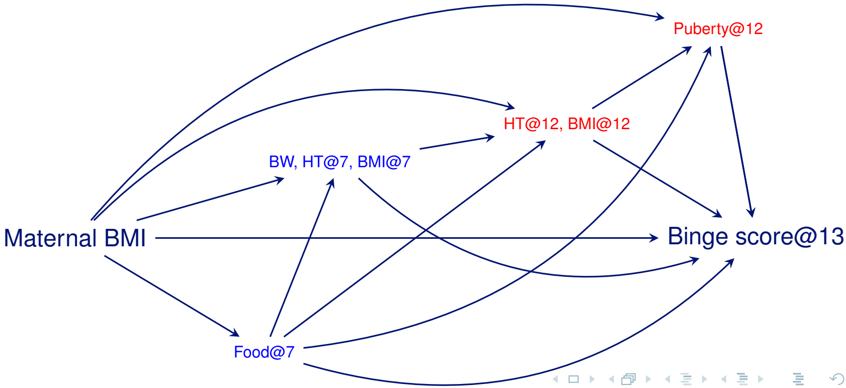
TCE	0.149	(0.079, 0.218)
NDE	0.059	(-0.019, 0.137)
NIE	0.090	(0.026, 0.153)



2. Sequential mediation

Early or late factors?

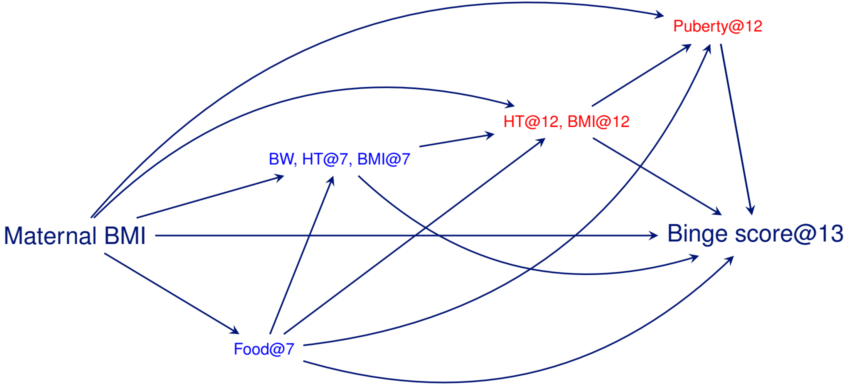
TCE	0.147	(0.081, 0.213)
NIE via M_1 and downstream	0.054	(0.006, 0.102)
NIE via M_2 only	0.034	(0.002, 0.066)



3. Interventional effects

Early or late factors?

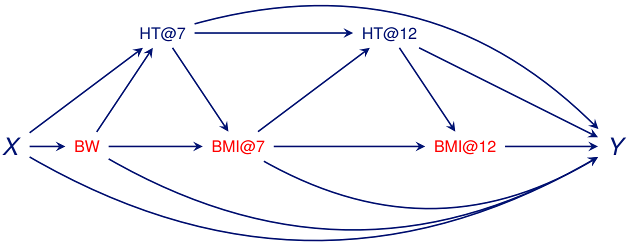
TCE	0.148	(0.096, 0.200)
RIA-NDE	0.059	(-0.001, 0.119)
RIA-NIE via M_1 and upstream	-0.009	(-0.054, 0.035)
RIA-NIE via M_2 and upstream	0.101	(0.050, 0.151)
RIA-NIE via M_1-M_2 dependence	0.002	(-0.006, 0.009)



4. Interventional effects

Which aspect of growth?

TCE	0.144	(0.091, 0.203)
RIA-NDE	0.063	(-0.008, 0.134)
RIA-NIE via BW and BMI	0.081	(0.035, 0.126)



Outline

Multiple questions

1. Do all mediators combined lead to a null direct effect?

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NDE	0.059	(-0.019, 0.137)
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- Dealing with multiple mediators involves additional complexities to those already faced with a single mediator of interest
- We may not be in a position to answer (all) the questions we wish to ask, especially when unmeasured confounding is suspected
- However interventional effects offer a useful new perspective as it relaxes the need for ordering and unconfoundedness of the mediators

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