Life course epidemiology:

From Bradford Hill's viewpoints to counterfactual comparisons

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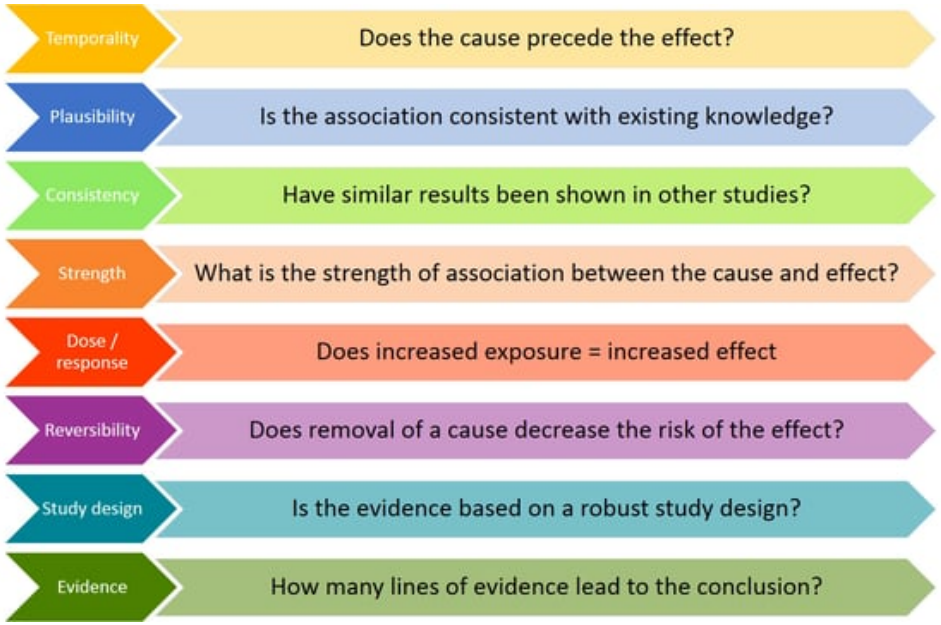
Austin Bradford Hill

The "criteria"

The environment and disease: association or causation? *Proc R Soc Med, 1965*

"**None of my nine viewpoints** can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non.*"



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- Many acute illnesses and chronic or recurring conditions that appear in later life are shaped by processes experienced in utero, childhood, adolescence or early adulthood.

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Later expanded into the developmental origins of health and disease (DOHaD) paradigms [Bianco-Miotto *et al.* 2017].

Complexities
Many dimensions

The field's strength is the recognition that origins of disease are complex [Ben Shlomo & Kuh, 2002] . . .

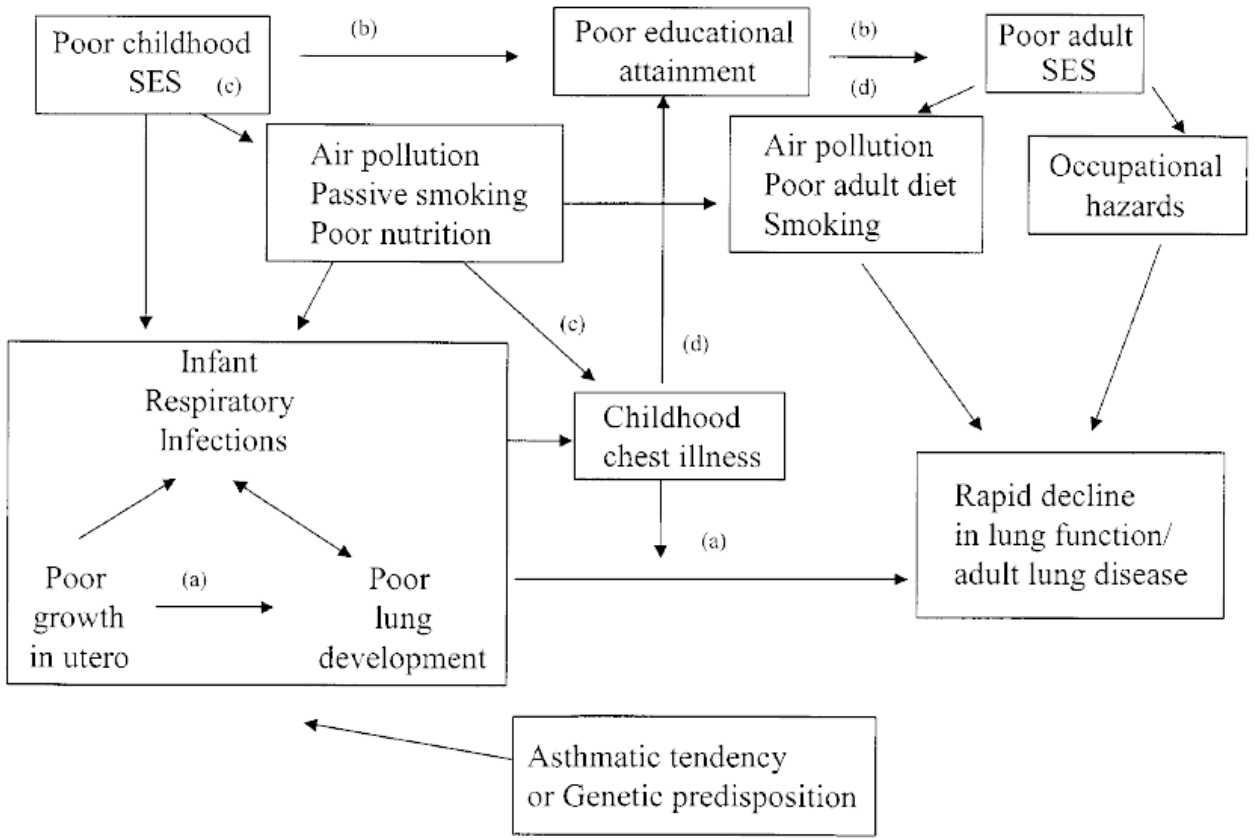
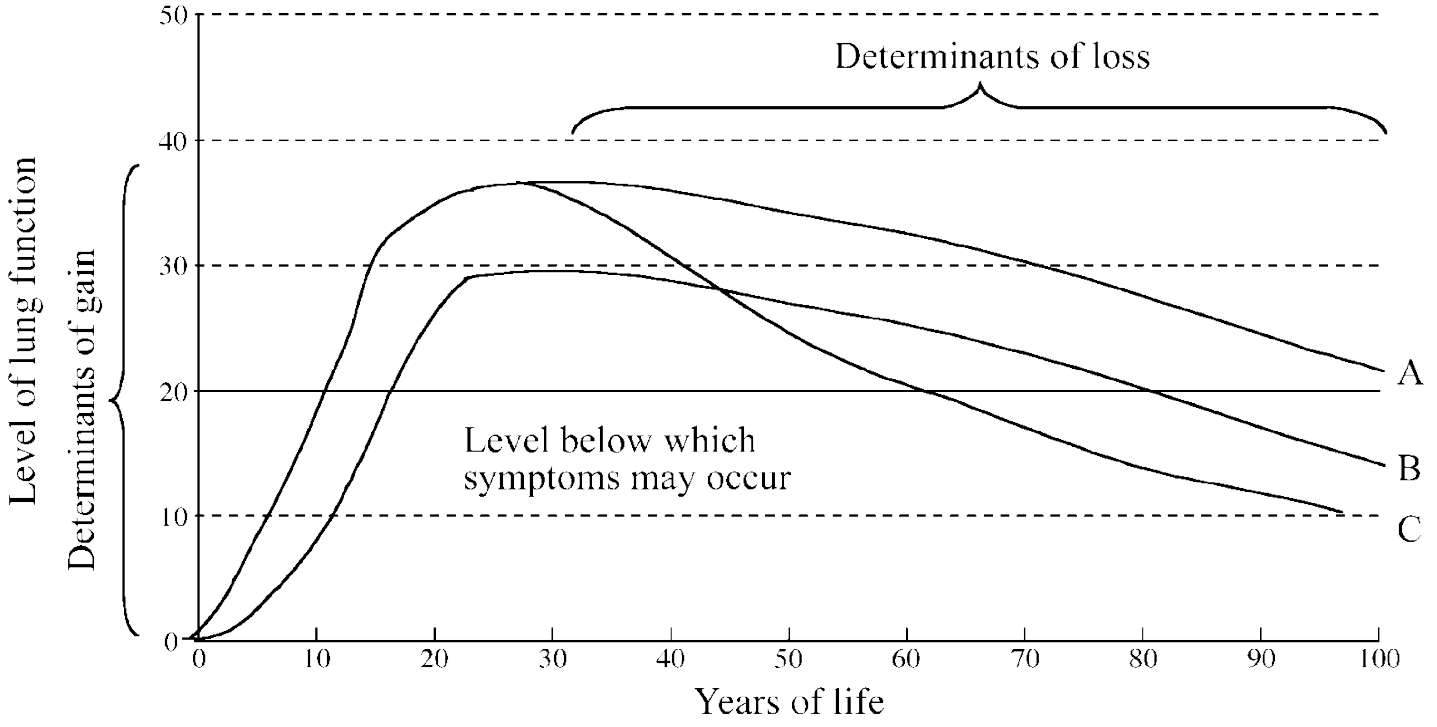


Figure 1 Schematic representation of biological and psychosocial exposures acting across the life course that may influence lung function and/or respiratory disease

Complexities
Time

. . . and involve time-varying exposures and outcomes.



modified from Strachan D. (1997)

Challenges

- Focus of life course investigations:
  - understand variations in disease and health across populations
  - devise interventions to prevent disease/ increase resilience.
- However, exposures:
  - arise in different periods (in utero, infancy, . . .);
  - most often vary in time;
  - might exert their influence during different phases in life;
  - are highly interconnected.
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Outline

1. Causal Questions
2. Counterfactuals
3. Example
4. Further Challenges
   - Multiple Pathways
   - Biases
5. Conclusions

Conceptual Models

- Consider a simplification of the earlier diagram whereby we ask whether respiratory illnesses in infancy and childhood influence adult lung function*:

- Several alternative possible generating mechanisms of what might be observed:
  - (a) Critical period model
  - (b) Cumulative exposure model
  - (c) Sensitive period model
  - (d) Pathways model

* While appropriately accounting for confounding induced by other life course paths.

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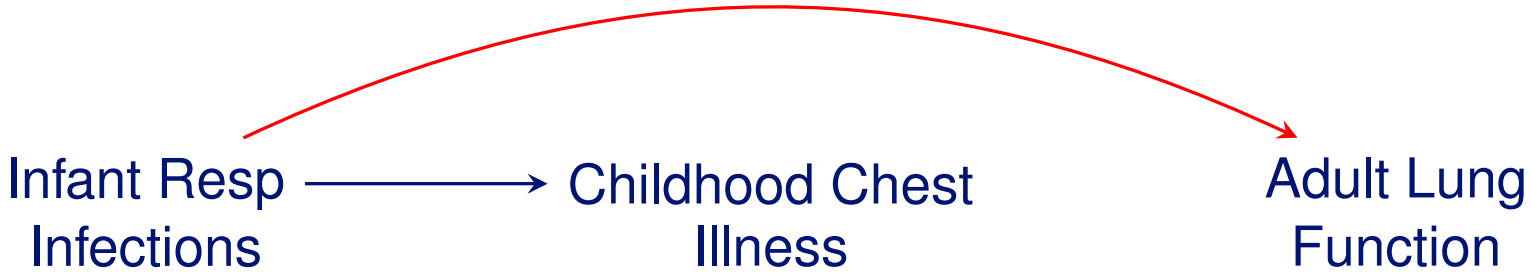

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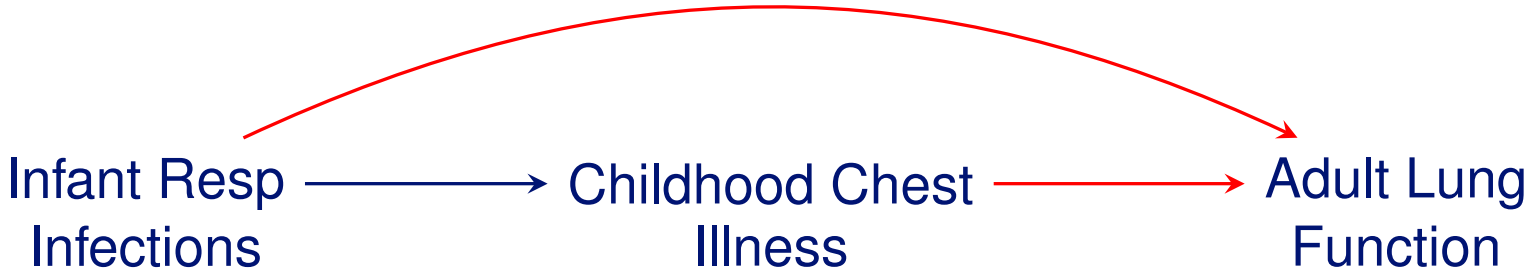

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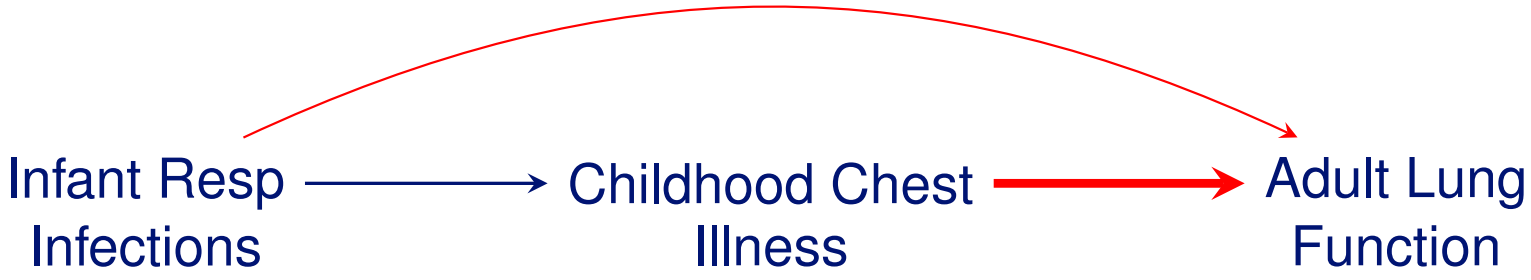

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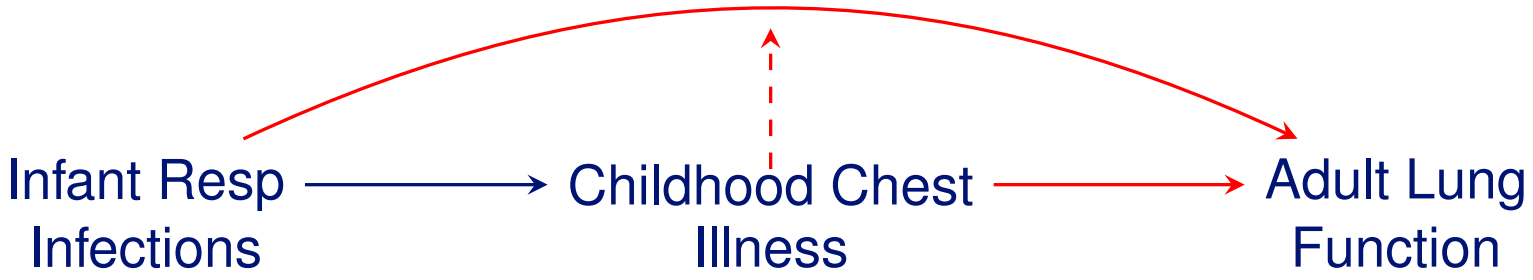

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- This involves fitting a regression model for the outcome (*e.g.* adult lung function) that includes all the relevant exposures, irrespectively of their time ordering.
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Counterfactual Reasoning

- Recent developments in causal inference offer several tools to deal with these challenges.
- Useful in this context is counterfactual thinking, which involves questions such as

"How would the world have been, had something been different?"

- We can formalise this question by:
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A short detour
Potential Outcomes

- Potential Outcomes: Let Y denote the outcome and A_1 and A_2 binary exposures of interest.
  - Then, we define $Y(a_1)$ as the potential outcome when A_1 is set to take the value a_1 (0/1).
  - Similarly, we define $Y(a_2)$ as the potential outcome when A_2 is set to take the value a_2 (0/1).
- We also define:
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A Selection of Causal Effects

Causal effects (*estimands*) can then be defined in terms of expectations ($E(\cdot)$) of these potential outcomes for the population of interest [†]:

- Total causal effects (TCE):

$$\begin{aligned} \text{TCE}_1 &= E\{Y(a_1 = 1)\} - E\{Y(a_1 = 0)\} \\ \text{TCE}_2 &= E\{Y(a_2 = 1)\} - E\{Y(a_2 = 0)\} \end{aligned}$$

These are comparisons of alternative hypothetical worlds that allows us to capture the notion of causal effects.

- Controlled direct effect (CDE) of A_1, when we set the later exposure A_2 to take the value a_2, as

$$\text{CDE}_1(a_2) = E\{Y(a_1 = 1, a_2)\} - E\{Y(a_1 = 0, a_2)\},$$

In these alternative hypothetical worlds A_2 does not change, capturing the sole effect of A_1 that does not involve A_2.

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Revisiting the Conceptual Models

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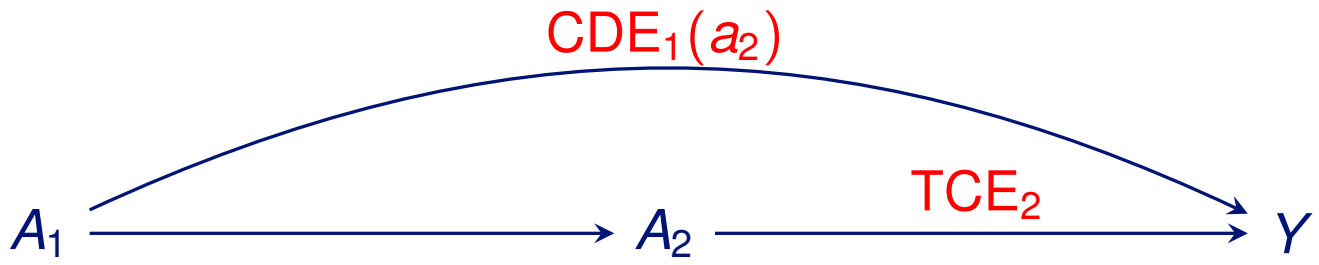

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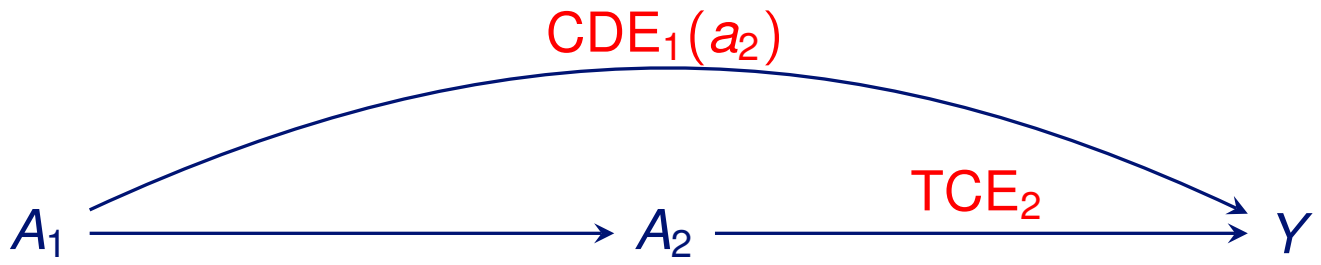

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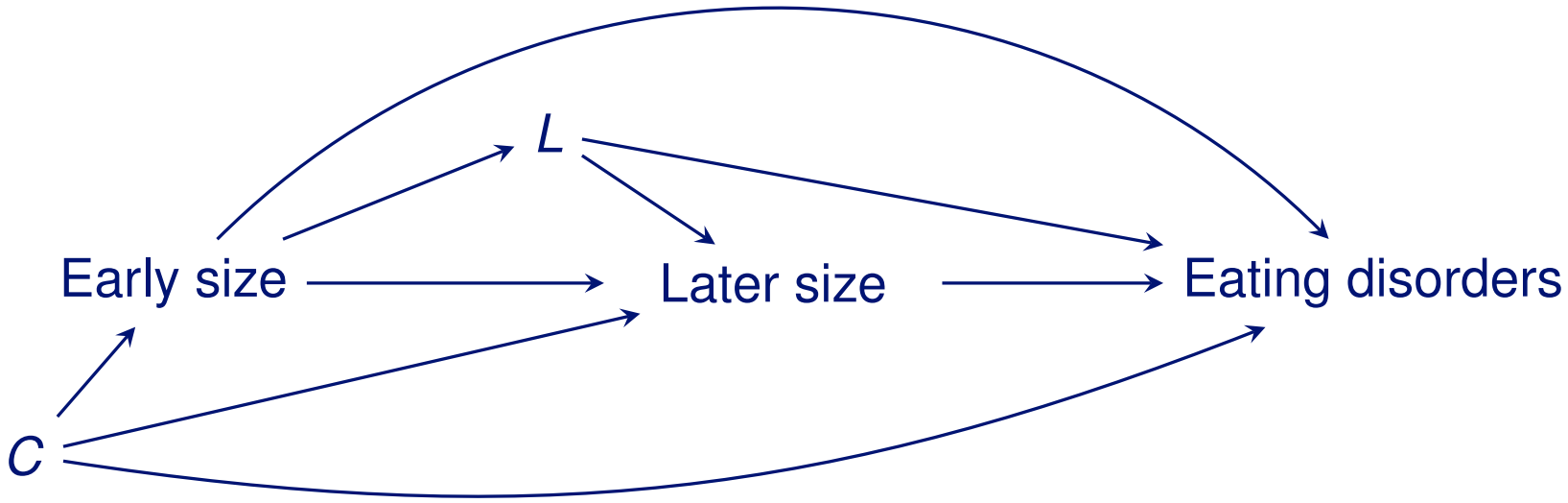
Eating Disorders in Adolescence

Avon Longitudinal Study of Parents And Children (ALSPAC) Study

- Associated with greater body size from birth to childhood [Zehr et al. 2007; Nicholls and Viner 2009]



- To devise preventive strategies, useful to identify whether there are critical or sensitive periods of growth:

- Data: 3500 girls from the ALSPAC Study:
  - Outcome: Binge/overeating score measured at 13y (parental reports).
  - Exposures[‡]: Birth weight and BMI from 7 to 12y (all standardized).

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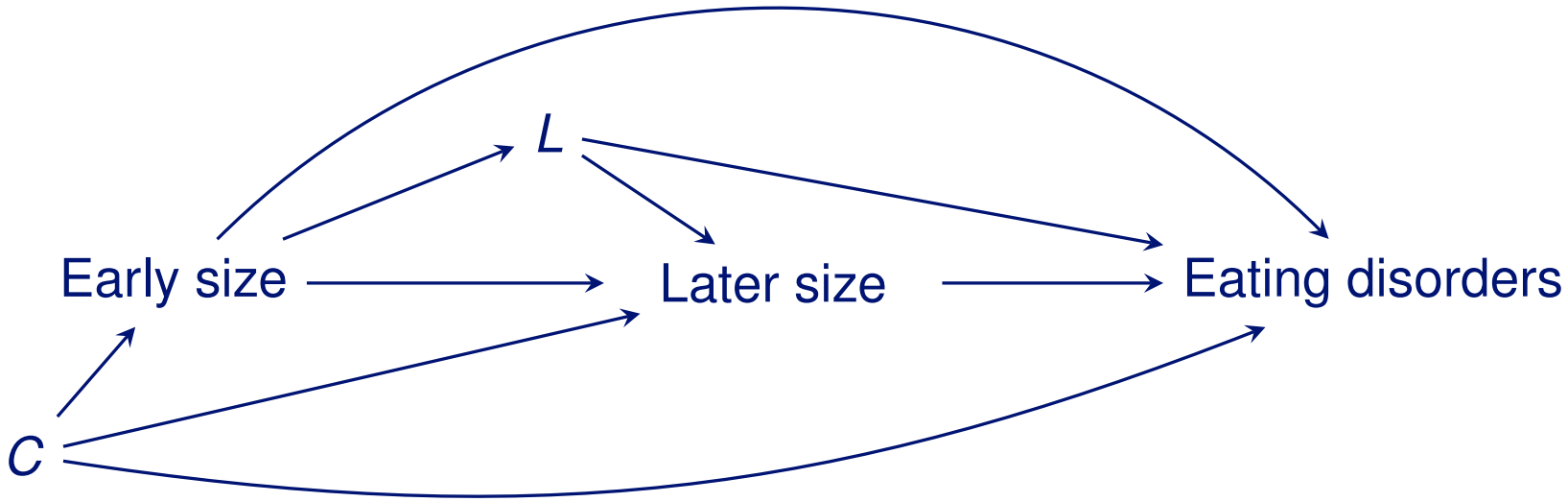

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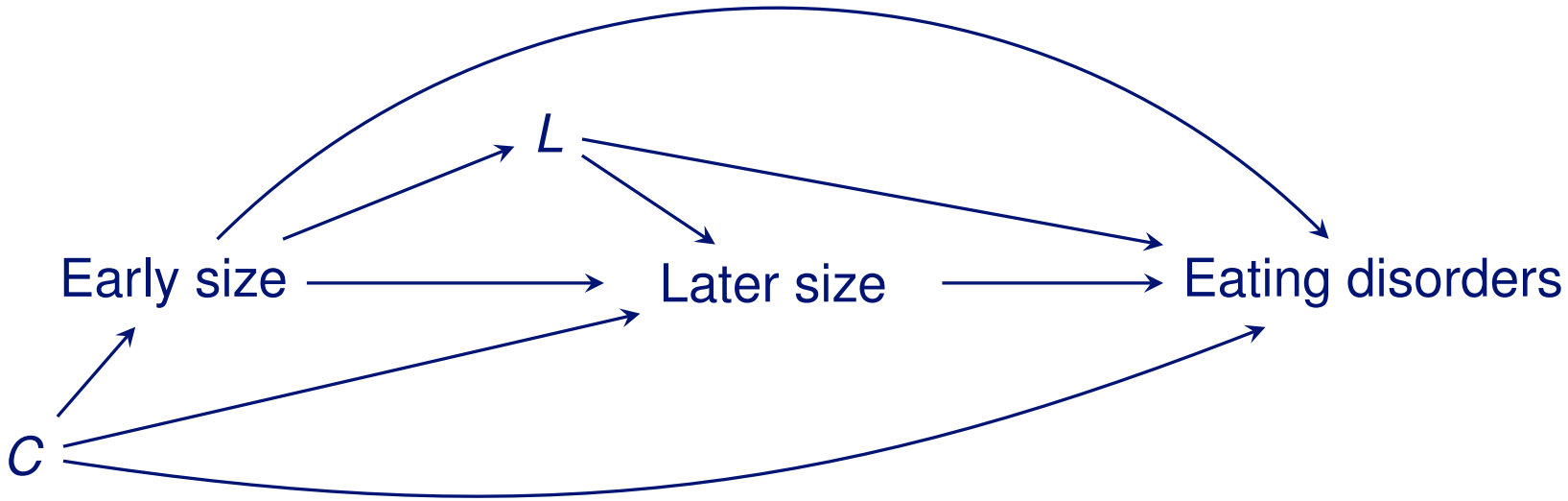

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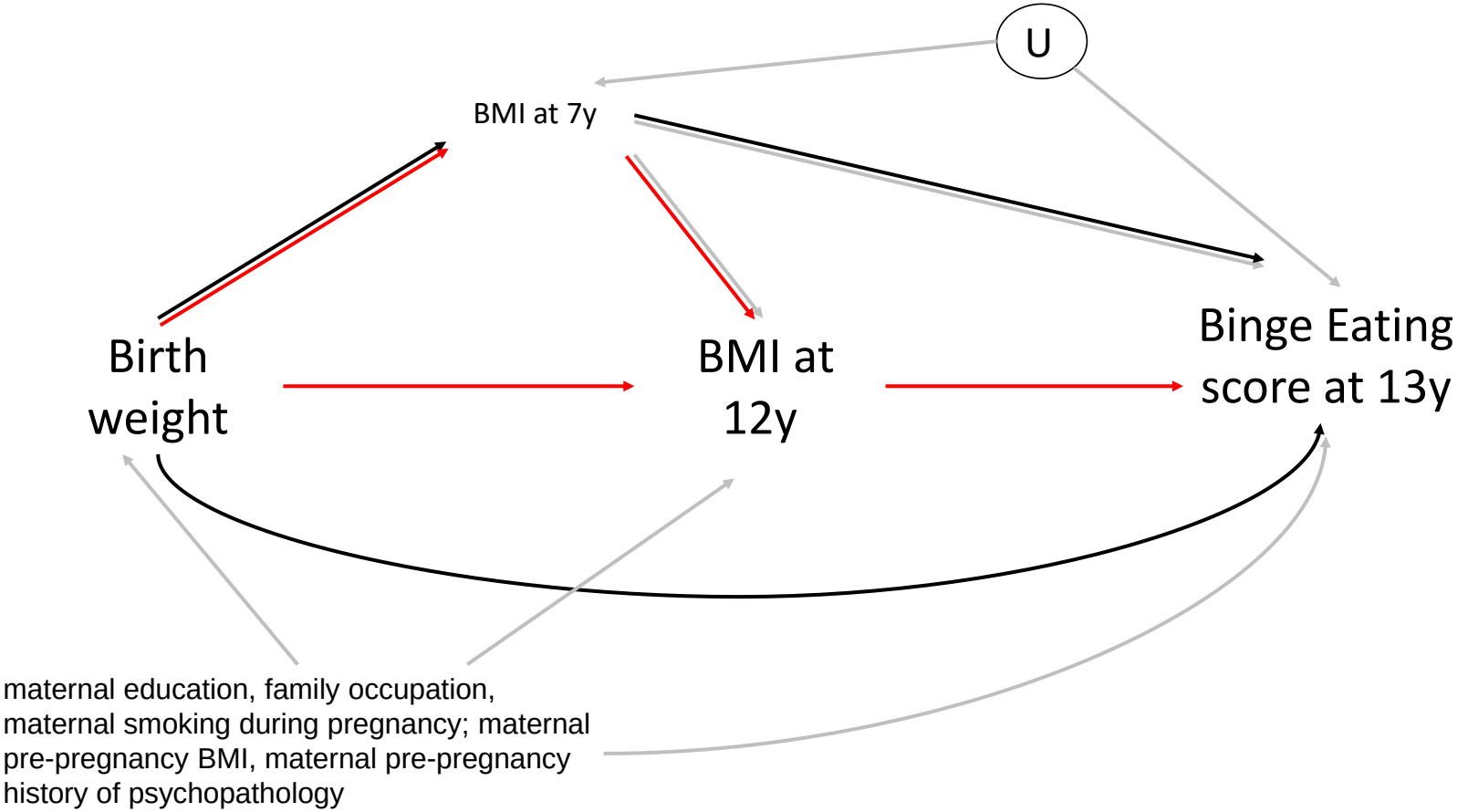

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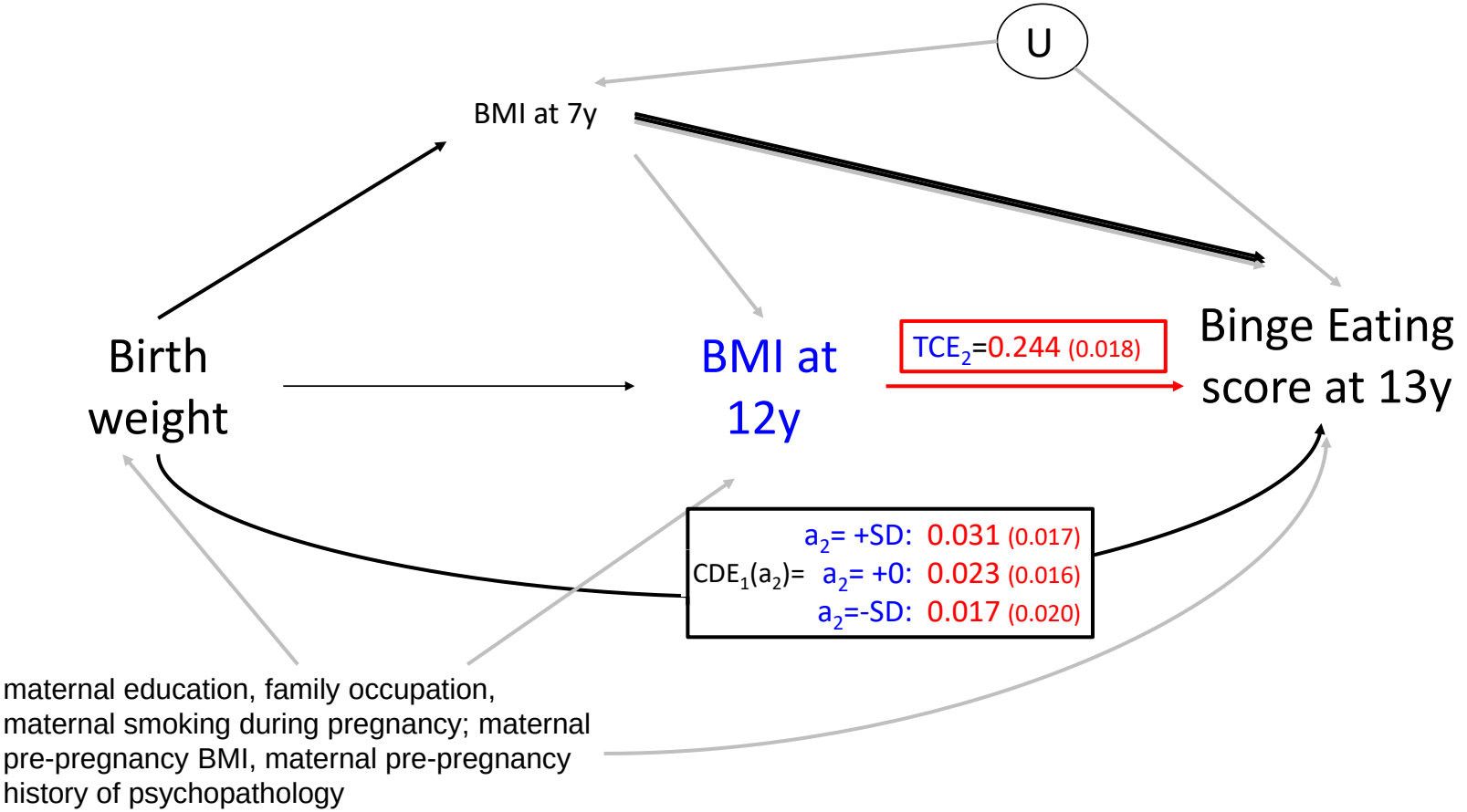

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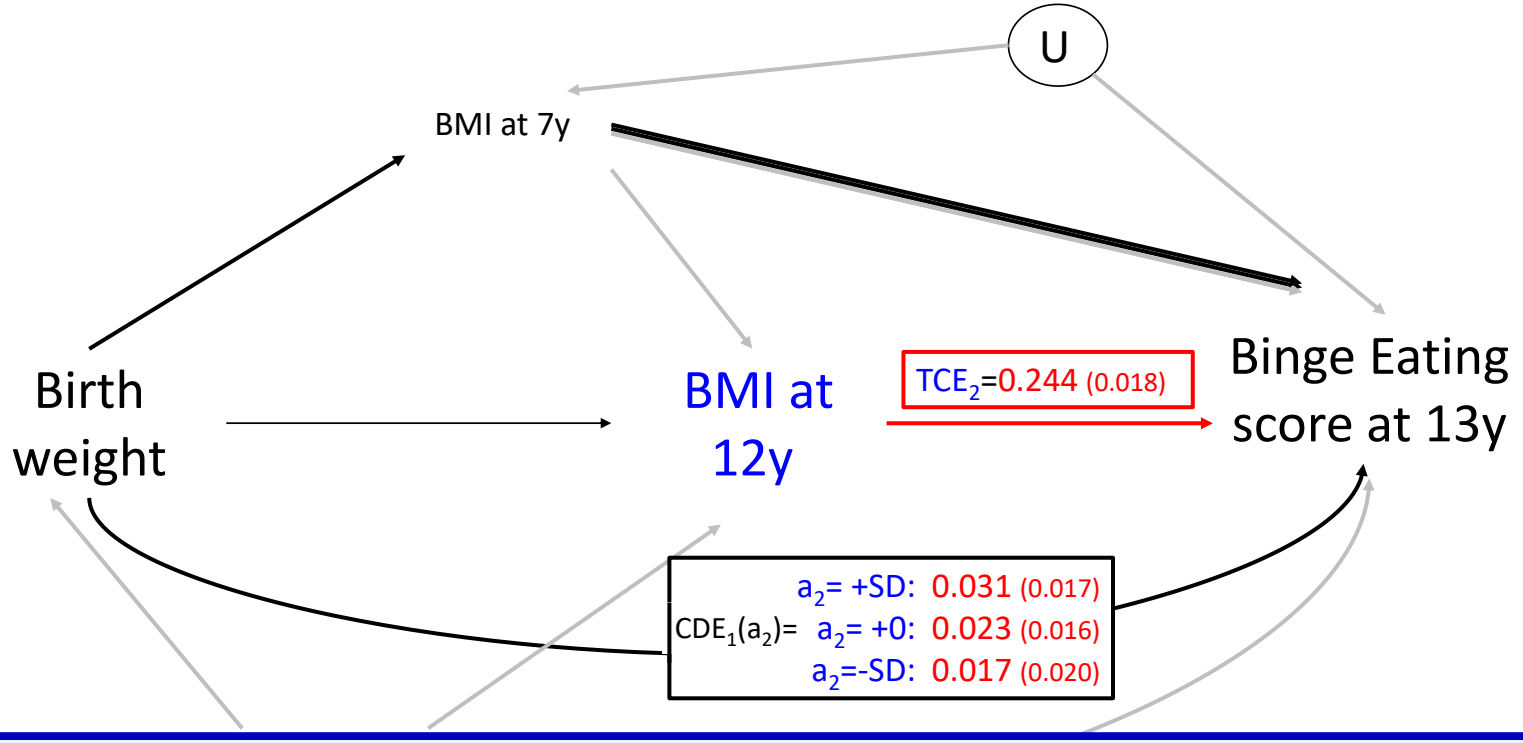

- Strong causal effect of BMI at 12y: critical period model?
- Some evidence for a pathway model.

Mechanisms

- *When might an intervention be most effective?*
- Although BMI at 12y has the strongest effect on the BE score, it is the most proximal and possibly the less amenable to interventions.
- We might consider interventions that are further upstream and ask:

  What would be the consequences of changing the distribution of BMI at 12 by intervening earlier in the life course?
- To address this sort of questions we could use direct and indirect interventional effects [VanderWeele *et al.* 2014].

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Another Short Detour

Interventional Direct and Interventional Indirect Effects

- Interventional effects are defined in terms of mean potential outcomes where again we intervene or not on A_1 and A_2 but this time the focus of our interventions is in terms of distributions for A_2.
- Formally, we define the mean potential outcome with the form[§]:

$$E\left\{Y\left(A_1 + s_1, \tilde{A}_2^{A_1+s_2}|\mathbf{C}\right)\right\},$$

where s_1 and s_2 take value 0 or σ ($\sim$ indicates that it is a random draw.).

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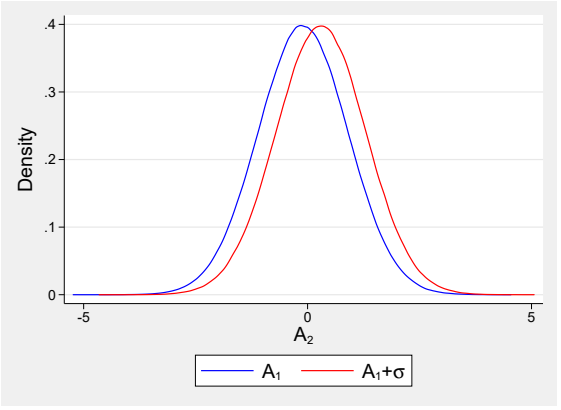
Distributions of A_2 that would arise had A_1 been (or not) shifted up by σ:

(ignoring C for simplicity)



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- Interventional effects are contrasts where it is the distribution of A_2 that is hypothetically manipulated.
- They call upon less stringent assumptions than the more intuitive natural direct and indirect effects (in particular: no requirement for intermediate confounding), with their sum capturing the total association of A_1 with Y.
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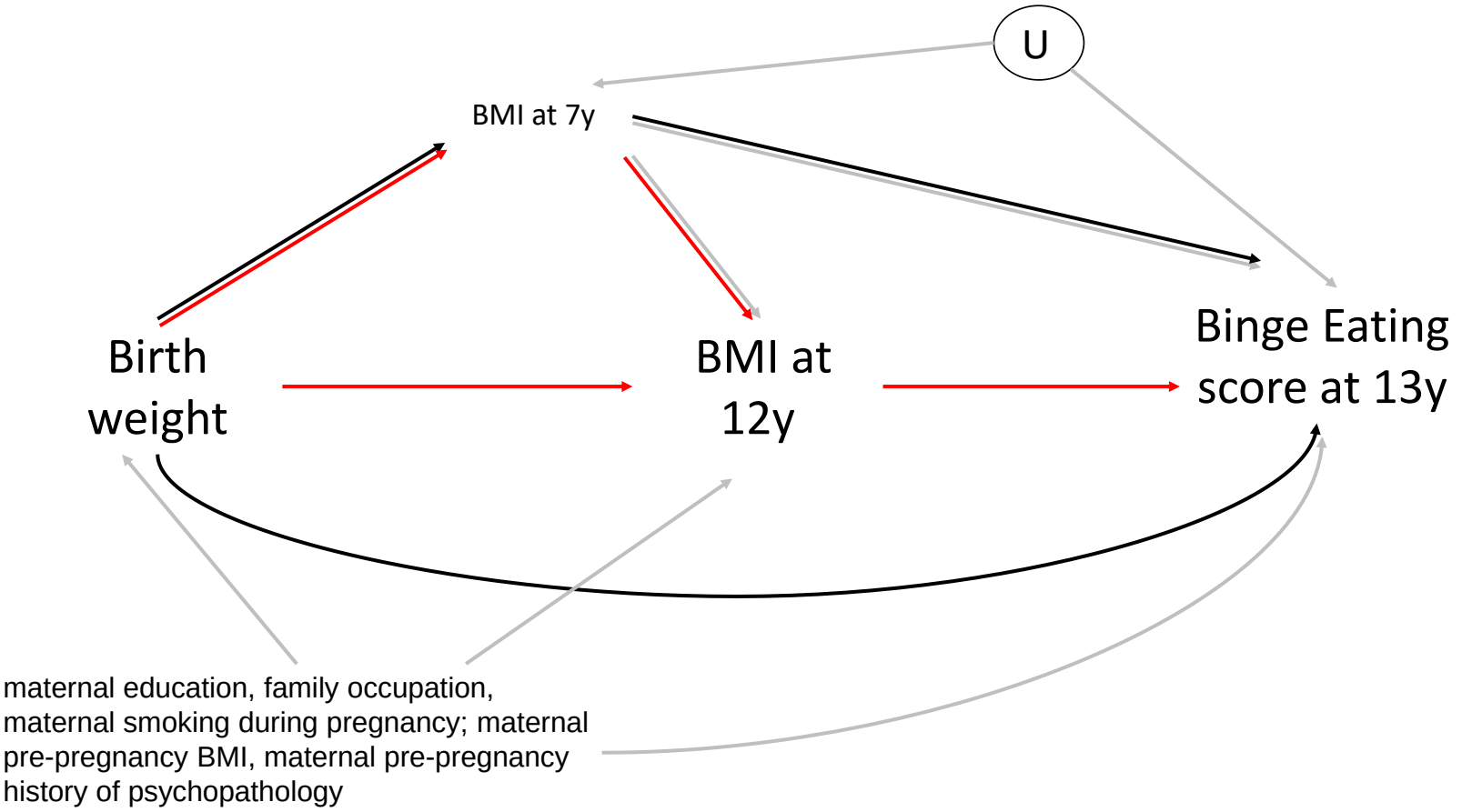
Eating Disorders in Adolescence

Part II: Interventional effects



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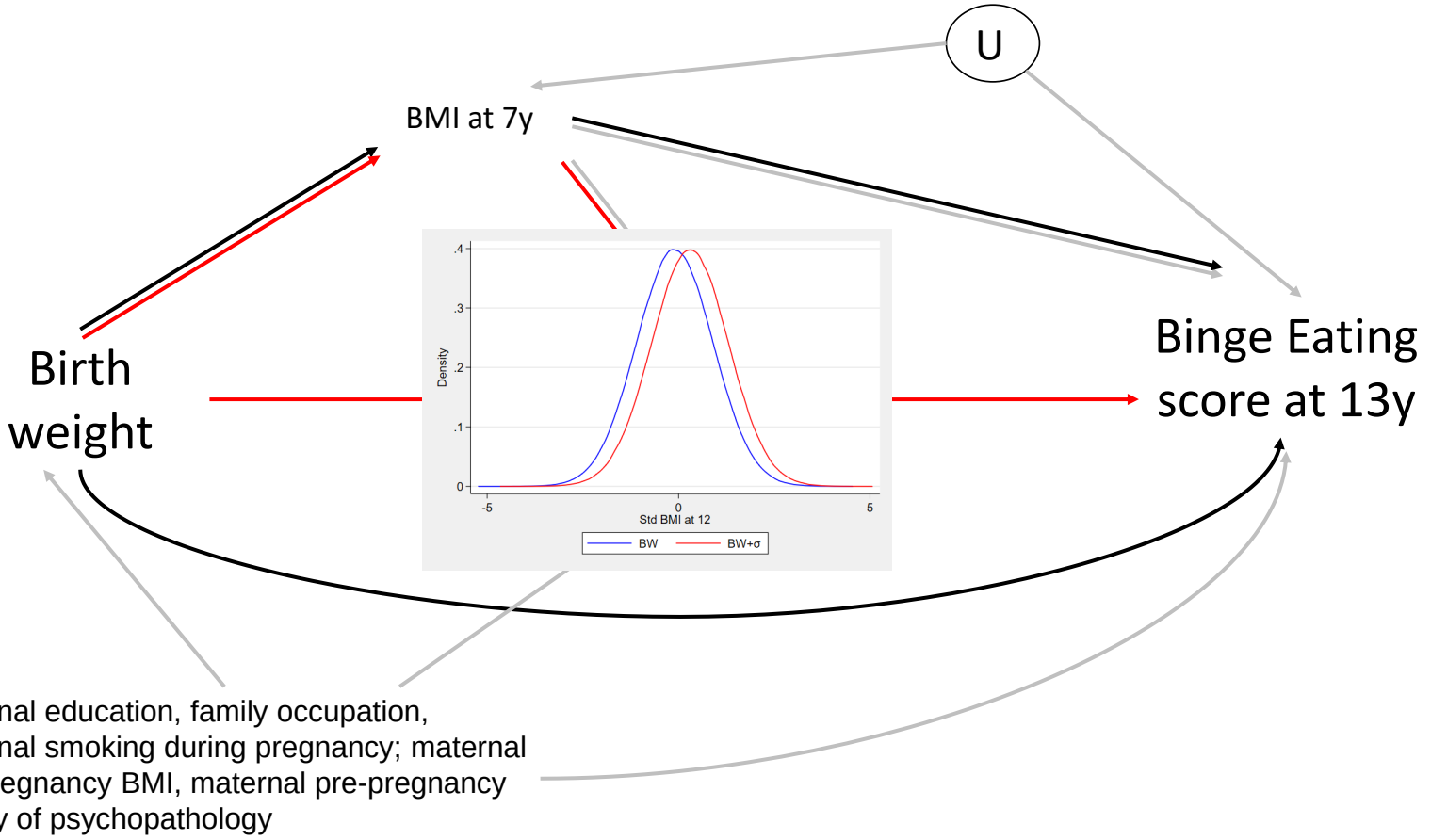

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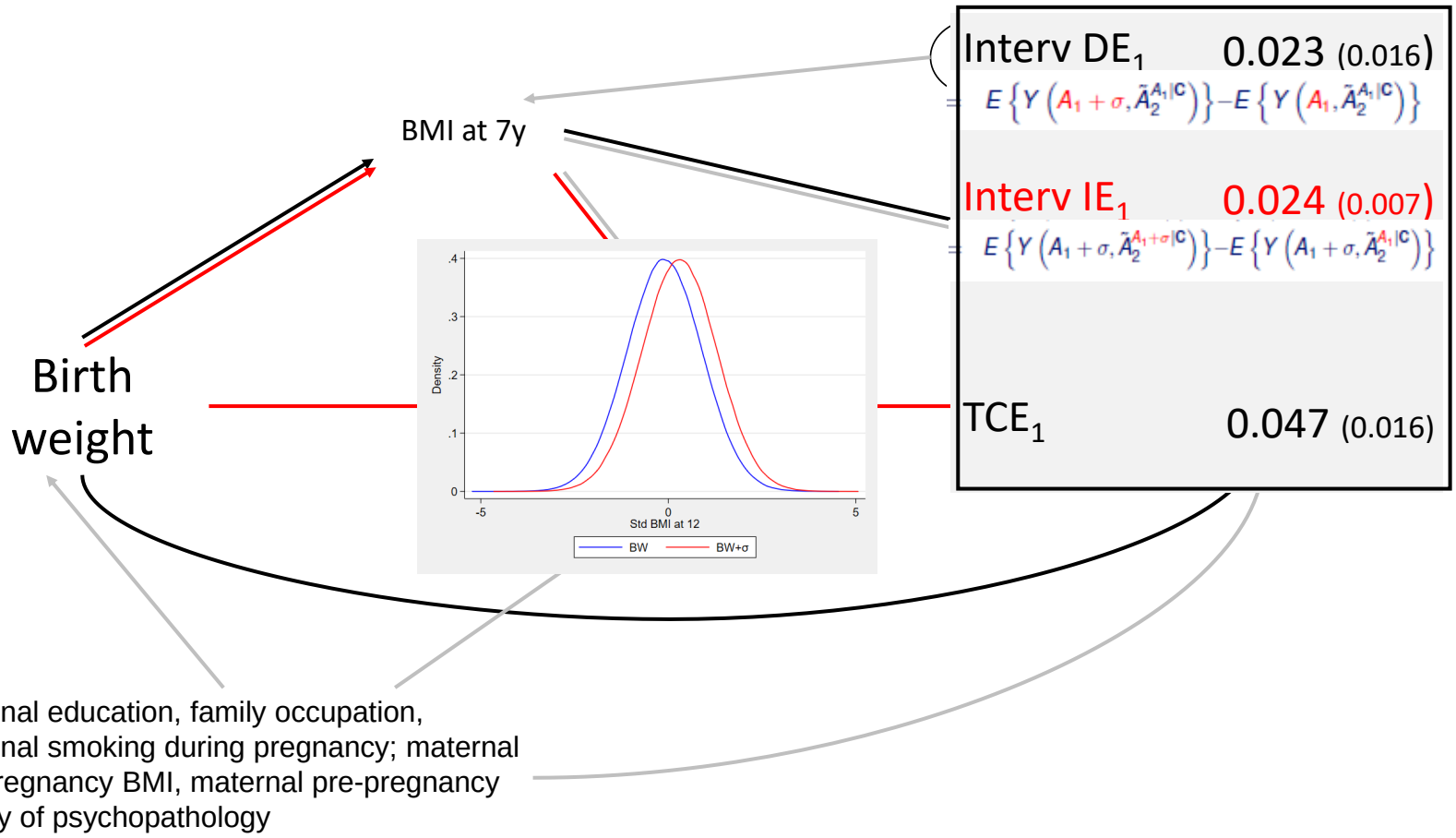

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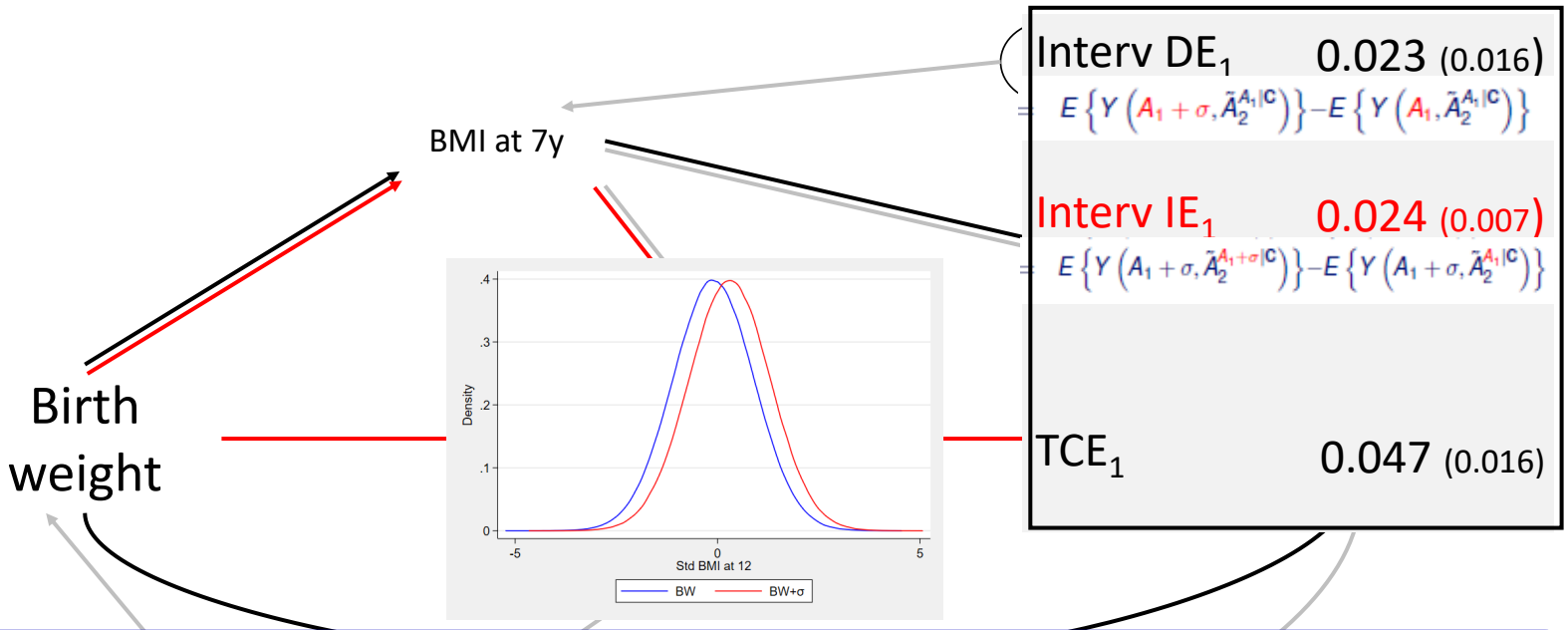

Interventional IE

Shifting the distribution of BMI at 12y by the same amount as if birth weight had shifted by 1SD, while holding birth weight fixed, would lead to increase binge eating by 0.024.

Eating Disorders in Adolescence

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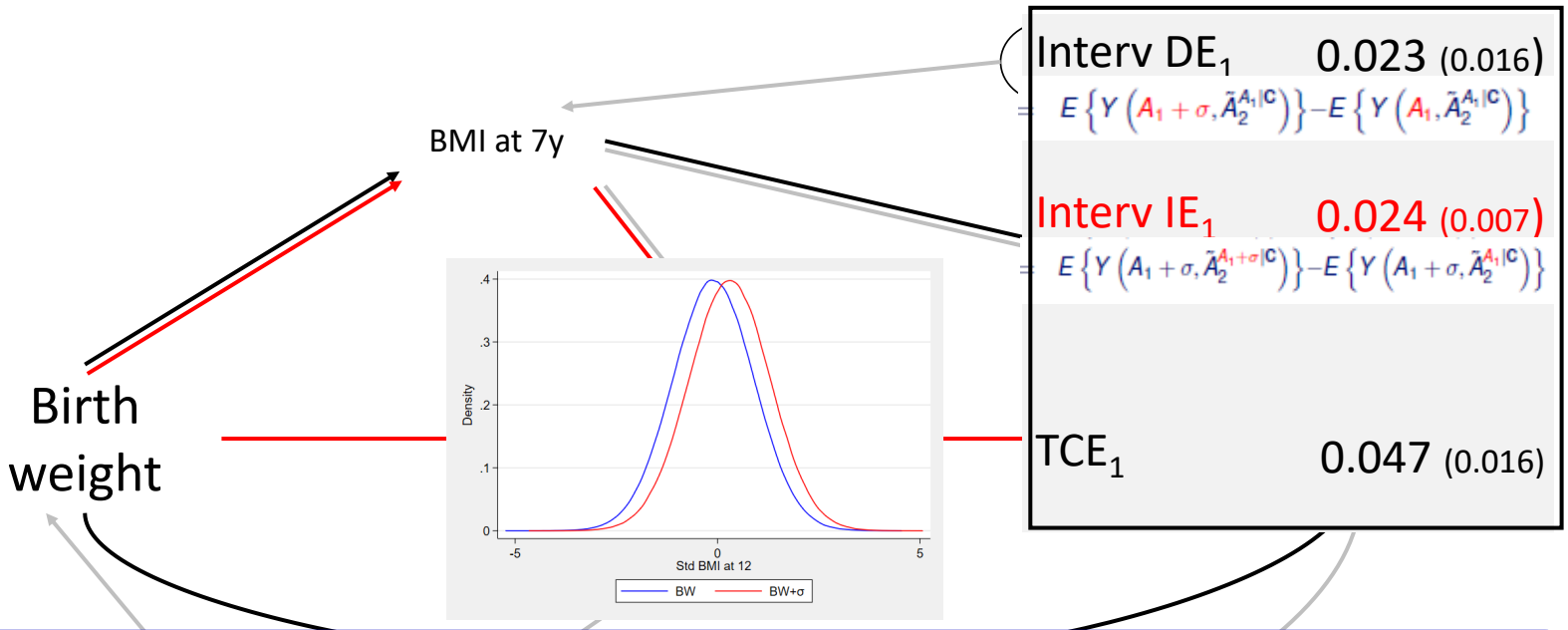

Interventional DE

Shifting birth weight by 1SD, while holding the distribution of BMI at 12y, would lead to increase binge eating by 0.023.

Further Challenges
Multiple Pathways

- Most life course investigations are more complex than this: they involve multiple interlinked and time-varying exposures.
- Understanding the pathways linking these exposures involves dealing with multiple mediators.
- This is hindered by our limited knowledge of how these variables are interconnected.
- However, a generalization of the interventional effects for multiple mediators [Vansteelandt and Daniel 2017, Micali *et al.* 2018] allows us to study these pathways without requiring us:
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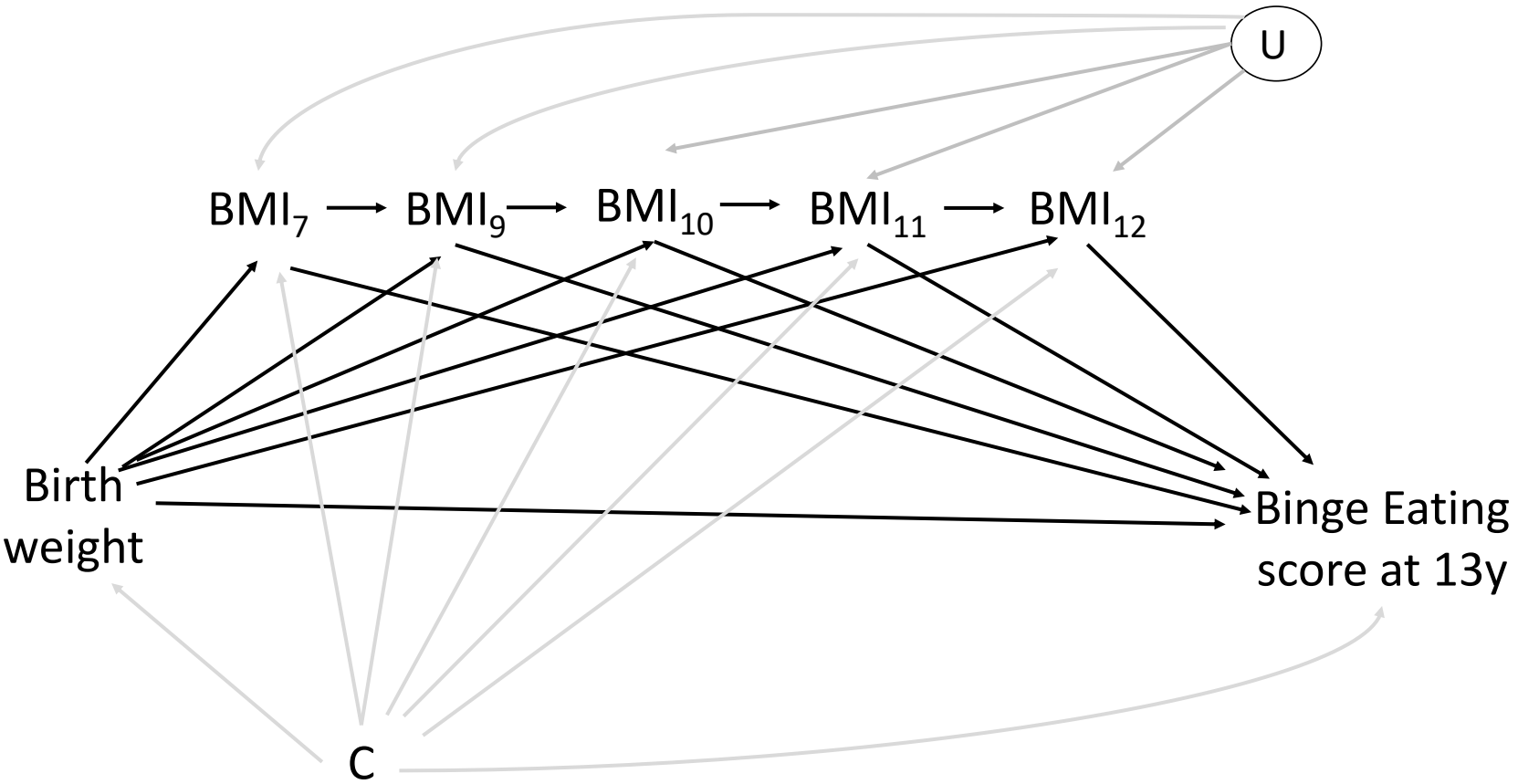
Eating Disorders in Adolescence

Part III: Multiple pathways

- Consider all repeated BMI measures from age 7 to age 12 jointly,
- and then separate early from late growth mediators:



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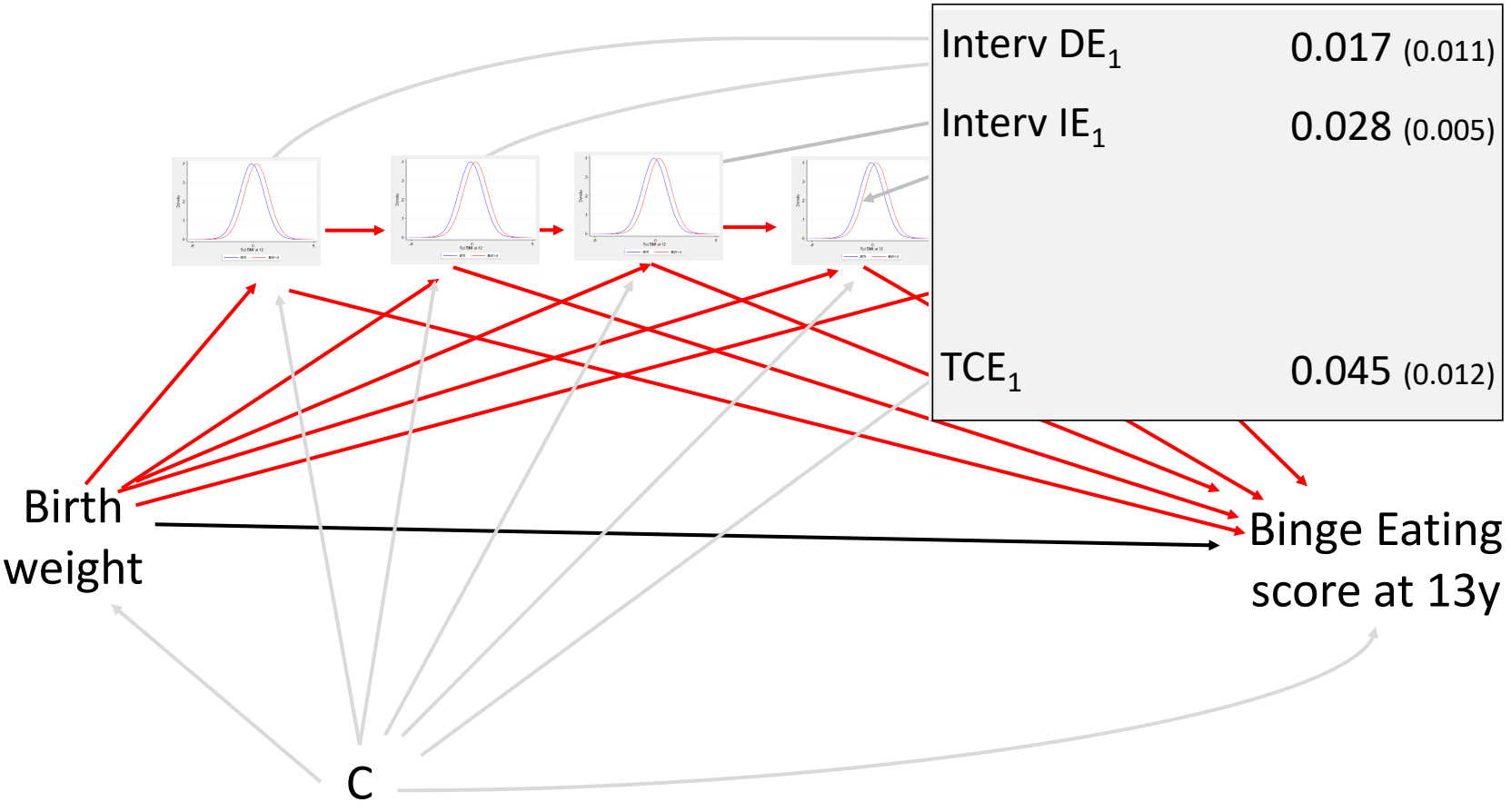

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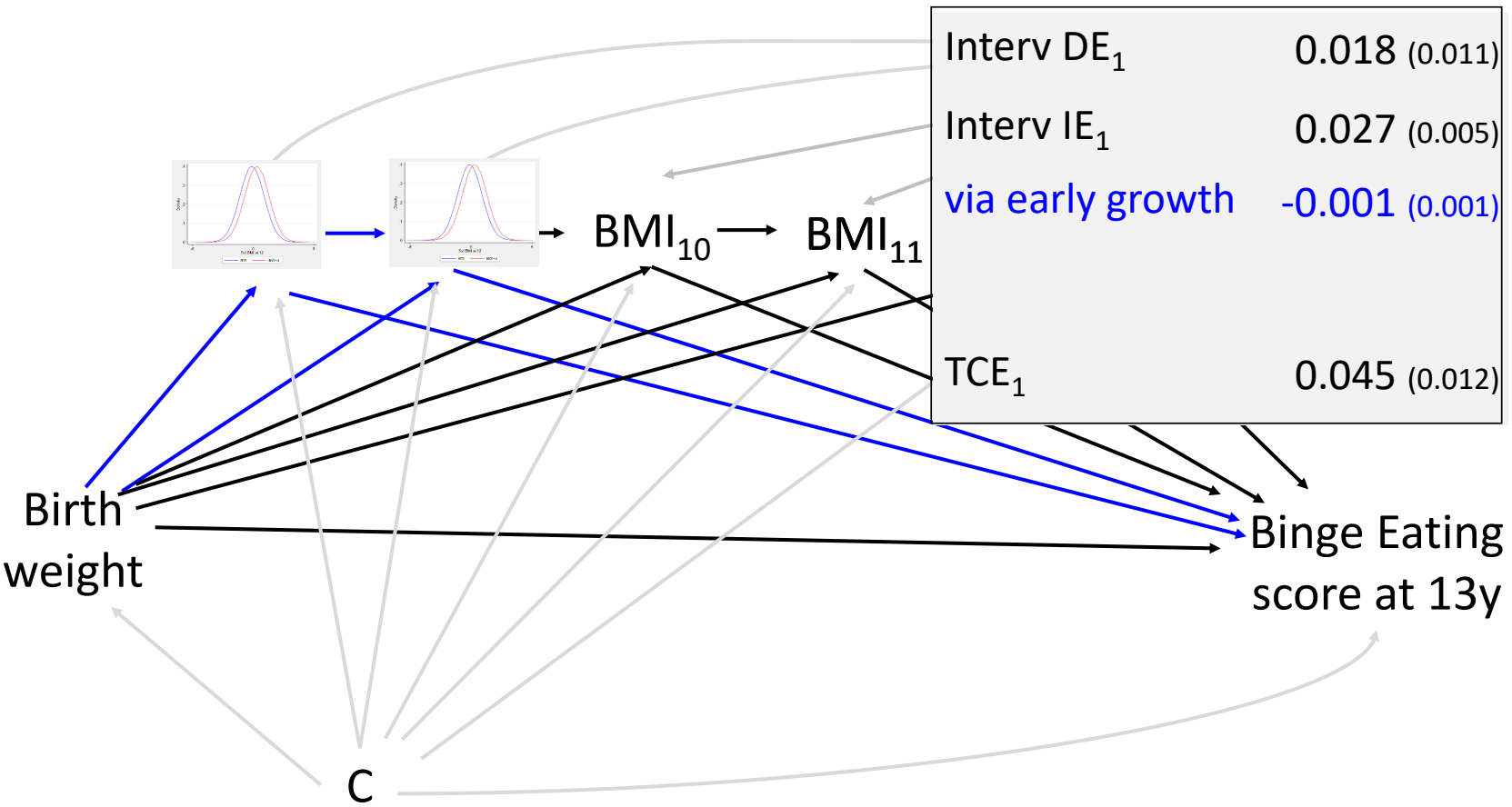

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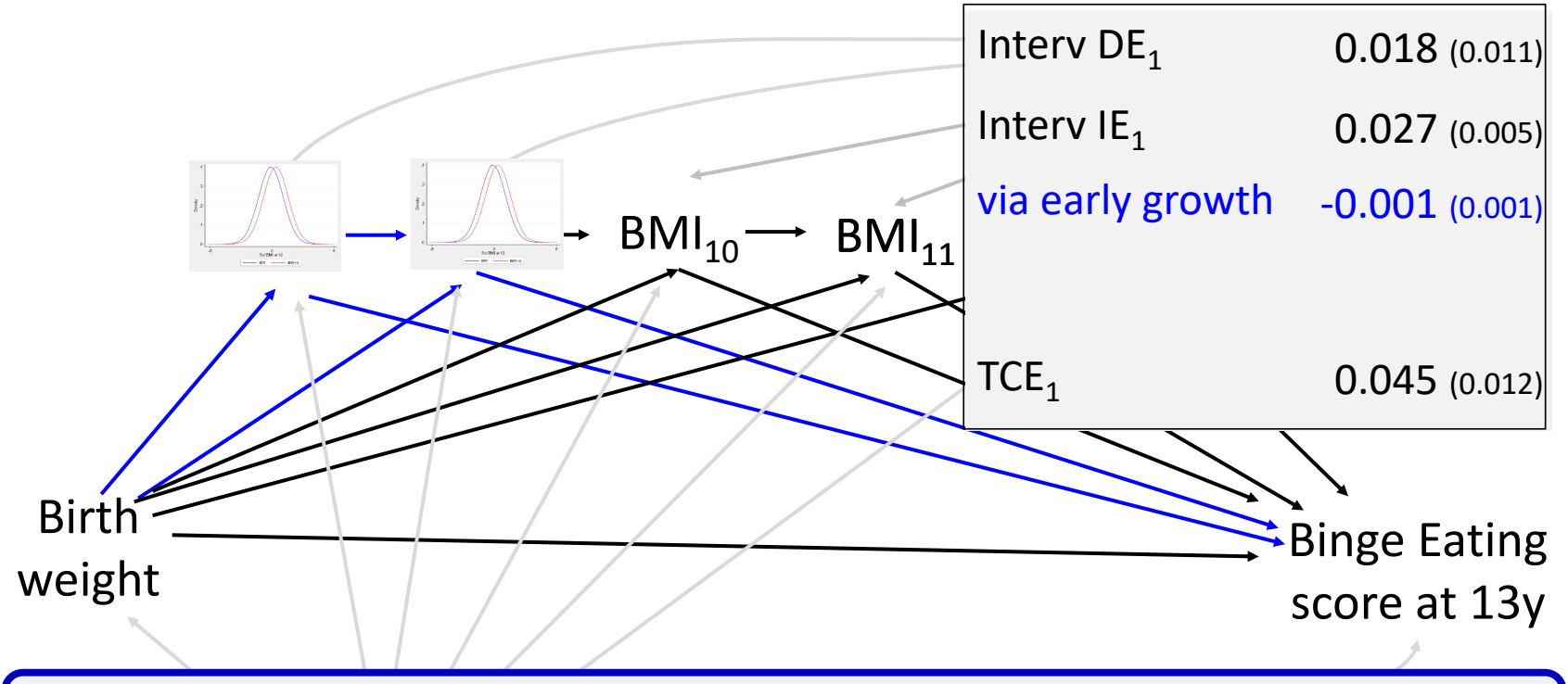

Early growth on its own does not contribute to the effect of shifting the joint distribution of BMI.

Potential Biases

- These results could be affected by bias, in particular:
  - Measurement error bias
    We can extend the model exploiting the repeated nature of the BMI observations.
  - Confounding bias
    Could do sensitivity analyses and/or adopt alternative study designs.

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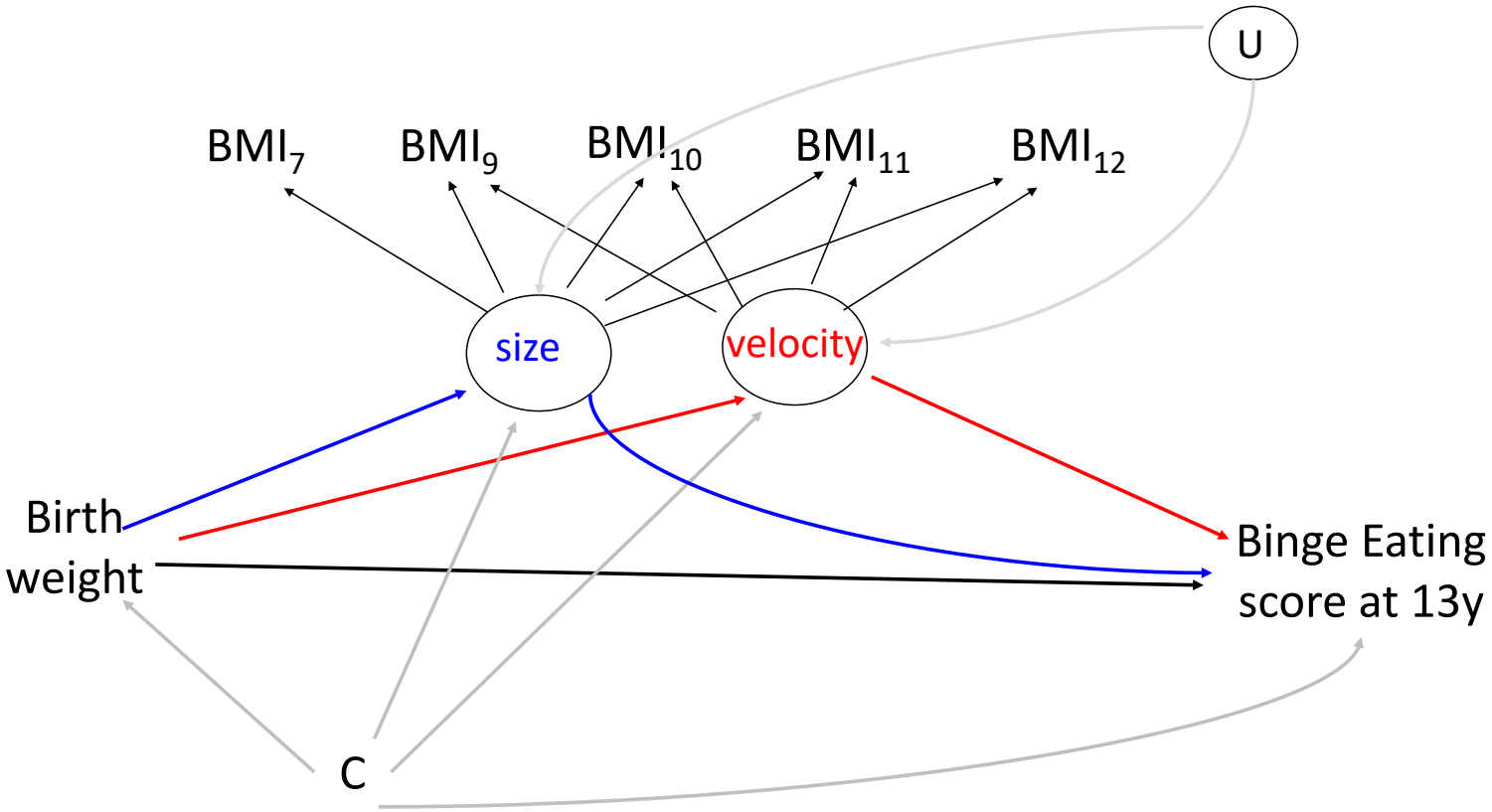
Revising the Example (once more)

- View the BMI observations as manifestation of latent growth features[¶] and derive their interventional effects [extending work by Sullivan *et al.* (2021)].



[¶] Random intercepts and slopes.

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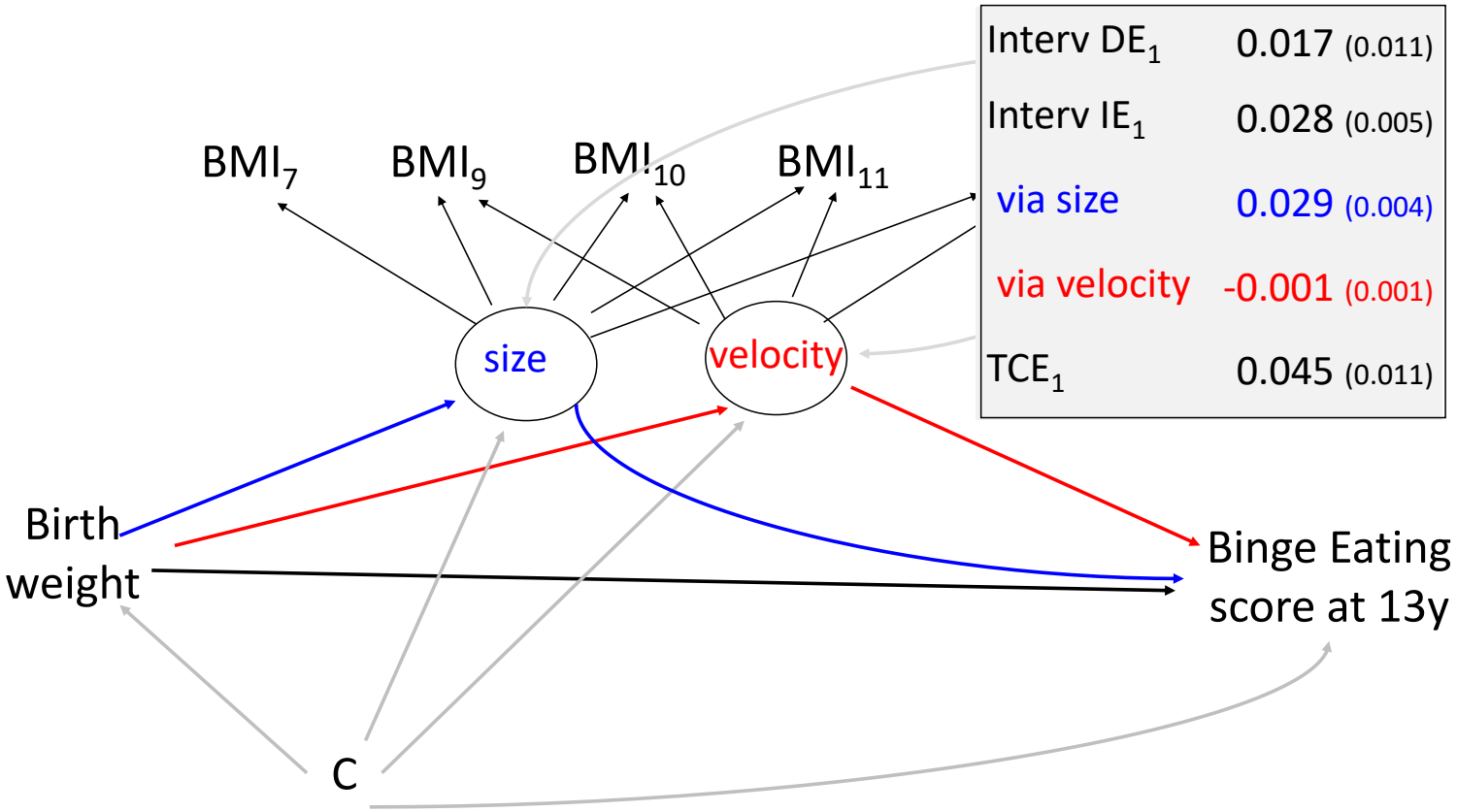

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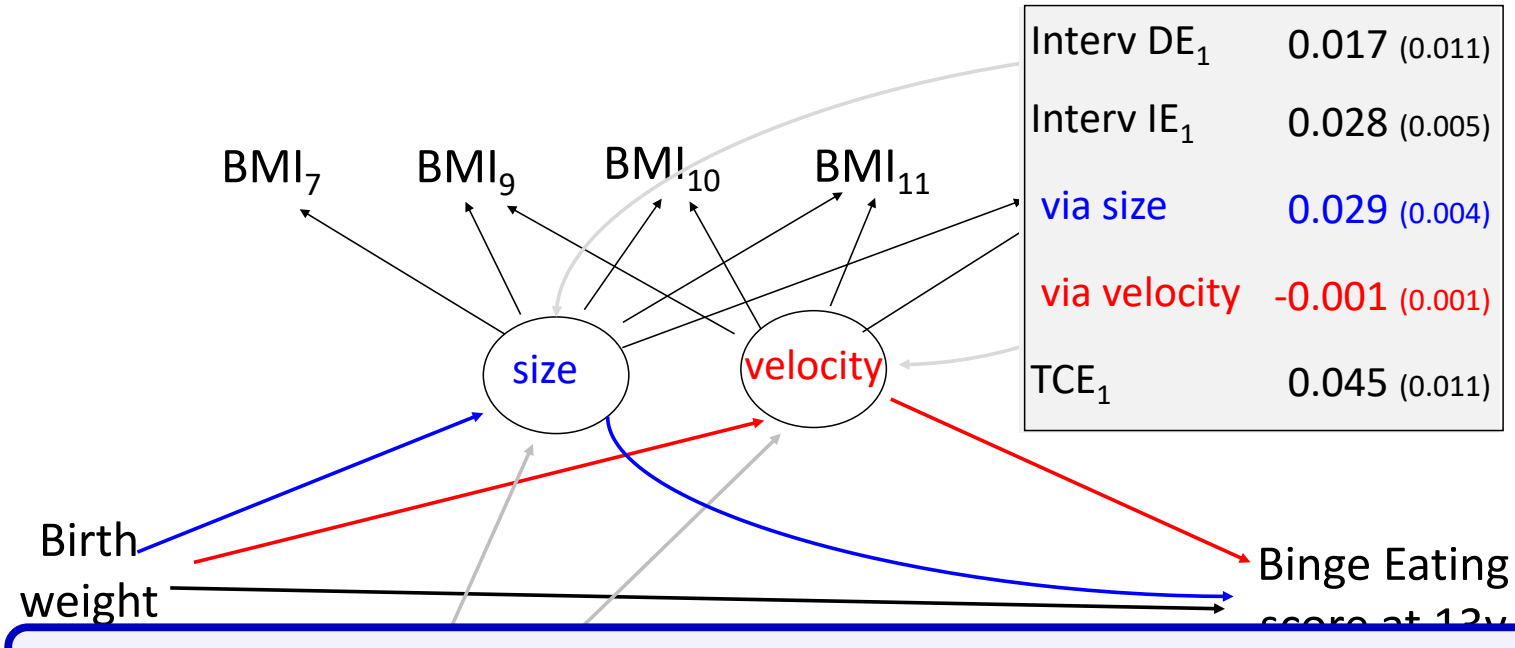

Latent size seems to be the most important feature leading to higher binge eating scores.

¶ Random intercepts and slopes.

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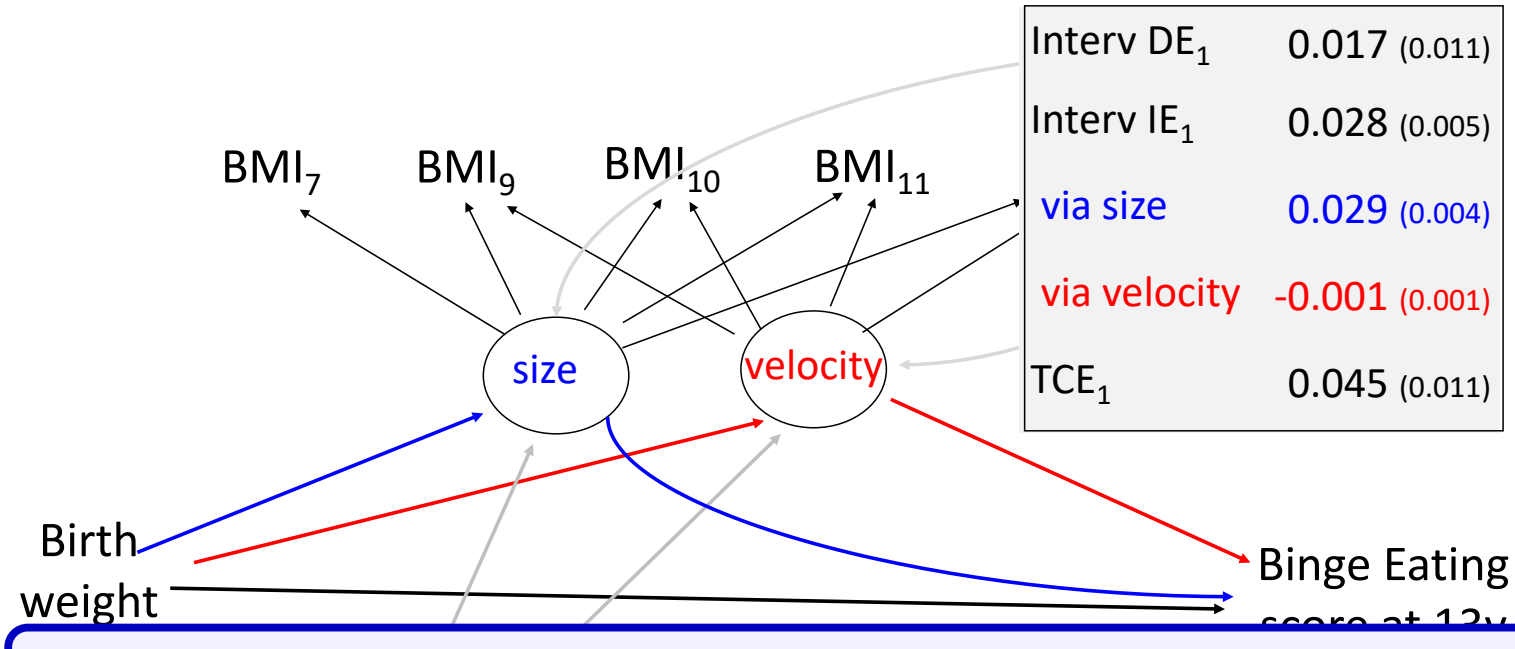

This clarifies earlier results on the (apparent) importance of BMI at 12y, and of the lack of influence of early size when it does not track.

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Confounding bias
Quasi-experimental designs

- To avoid the biases that would arise from incomplete controlling of confounding, researchers have found imaginative ways to proxy experimental conditions:
  - Sibling comparison studies
  - Mendelian randomisation (MR) studies.
- We ought to be caution with both when using them in life course investigations.

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Sibling Comparison Studies

Research report

Maternal smoking during pregnancy and offspring antisocial behaviour: findings from a longitudinal investigation of discordant siblings

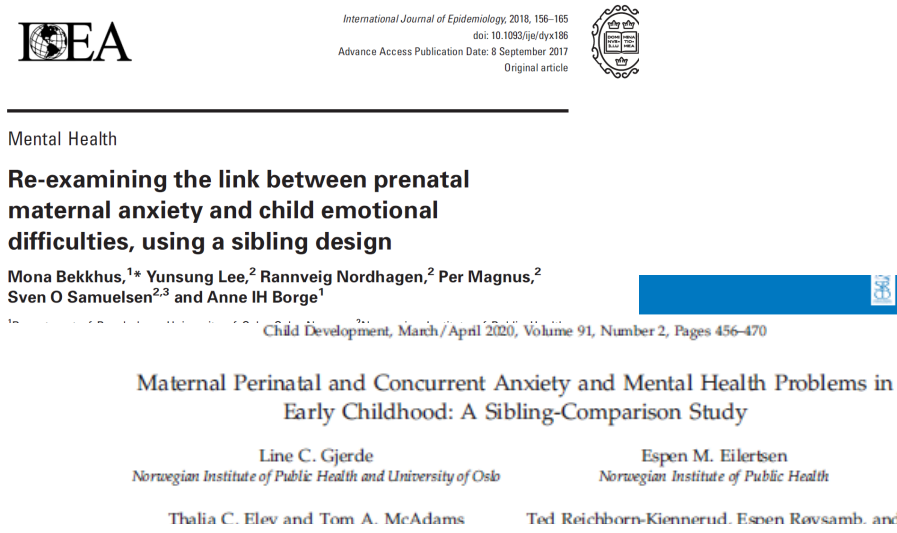
Angela D Paradis,[1] Edmond D Shenassa,[1,2,3] George D Papandonatos,[4] Michelle L Rogers,[5] Stephen L Buka[1]

Pediatric Neuroscience

Section Editors: Peter J. Davis/Gregory J. Crosby

Early Childhood Exposure to Anesthesia and Risk of Developmental and Behavioral Disorders in a Sibling Birth Cohort

Charles DiMaggio, PhD,*† Lena S. Sun, MD,‡ and Guohua Li, MD, DrPH*†



IJEA

International Journal of Epidemiology, 2018, 156–165
doi: 10.1093/ije/dyx186
Advance Access Publication Date: 8 September 2017
Original article

Mental Health

Re-examining the link between prenatal maternal anxiety and child emotional difficulties, using a sibling design

Mona Bekkhus,[1]* Yunsung Lee,[2] Rannveig Nordhagen,[2] Per Magnus,[2] Sven O Samuelsen[2,3] and Anne IH Borge[1]

Child Development, March/April 2020, Volume 91, Number 2, Pages 456–470

Maternal Perinatal and Concurrent Anxiety and Mental Health Problems in Early Childhood: A Sibling-Comparison Study

Line C. Gjerde
Norwegian Institute of Public Health and University of Oslo

Espen M. Eilertsen
Norwegian Institute of Public Health

Thalia C. Eley and Tom A. McAdams

Ted Reichborn-Kjennerud, Espen Røysamb, and

- They can be viewed as matched cohort studies where the matching removes shared genetic and shared (early) environmental factors.

Sibling Comparison Studies

- Sibling comparison should be free from confounding by factors that are constant within the pair.

Estimation proceeds as for standard matched designs where only discordant pairs contribute to the estimation.

- It is not generally highlighted however that [Sjolader *et al.* 2016;Petersen & Lange 2019; Frissel 2021]

(a) There can still be residual confounding from non-shared environmental factors as well as time-varying confounders.
(b) Different estimation methods target different estimands and populations:
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MR Studies

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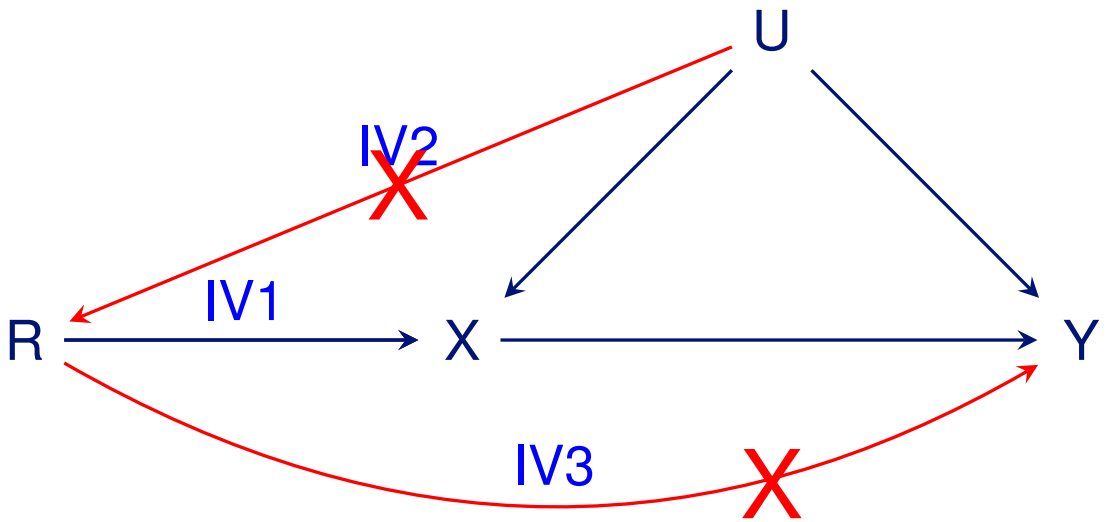
- The three core assumptions for a variable *R* to be an IV:



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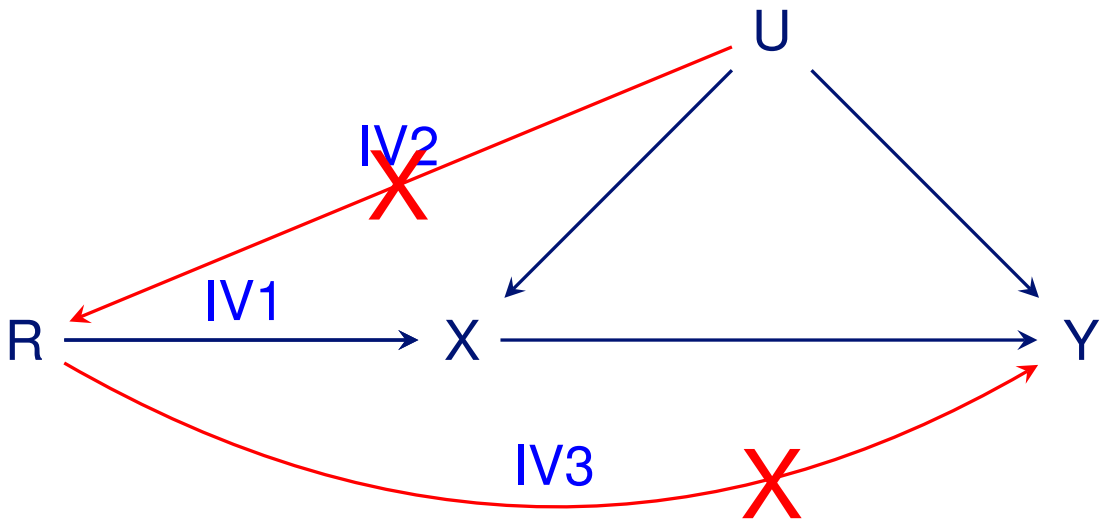

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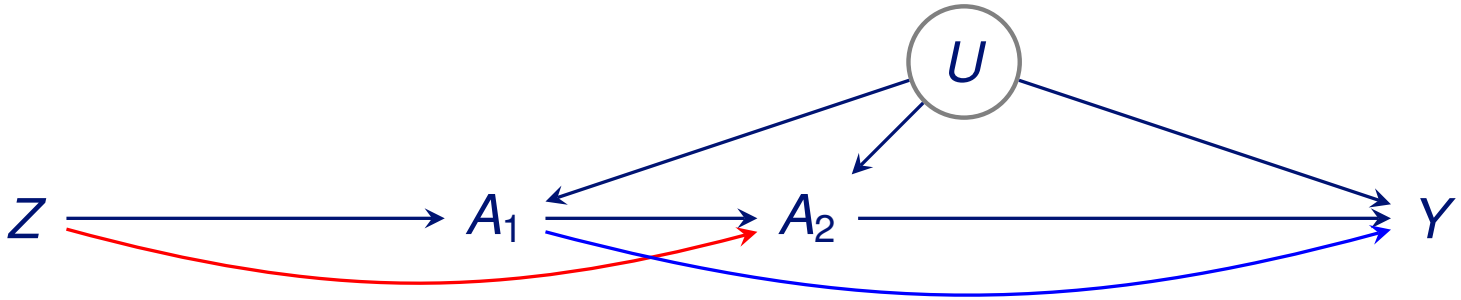
MR Studies and time-varying exposures



- When an exposure is time-varying, ER is most likely not met, even if we focussed on a particular time point [Lebreque *et al.* , 2019; Burgess *et al.* 2021]:
- If we wished to study the causal effect of A_1, for Z to be an IV the red arrow should be absent;
- If we wished to study the causal effect of A_2, for Z to be an IV the blue arrow should be absent.

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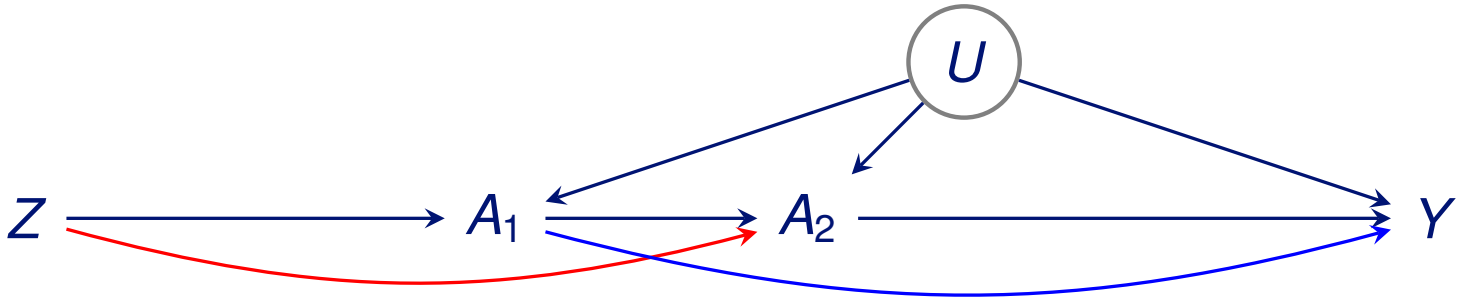

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Quasi-experimental study designs are to be judged as carefully as other types of observational studies!

How far are we from the viewpoints?

Then and now:

1. strength: confounding and sensitivity analysis
2. consistency: triangulation of evidence
3. specificity: use of negative controls
4. temporality: life course view-point
5. biological gradient: flexible modelling
6. plausibility: substantive knowledge . . .
7. coherence: . . . stated in DAGs
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A logical continuum but currently with greater focus on a more precise definition of what effect is being targeted.

Final thought

Thanks

- This is joint work with *Andrew Pickles* and *Moritz Herle*.
- Thinking on these topics comes from long-term collaborations with *Rhian Daniel* and the *STRATOS Causal Inference Topic Group* (*Els Goetghebeur*, *Saskia le Cessie*, *Ingeborg Waernbaum*, *Vanessa Didelez*, and *Erica Moodie*), and many conversations with *Stijn Vansteelandt*.
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