Hygienic thinking and exotic methods

Bianca L. De Stavola

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LONDON SCHOOL *of* HYGIENIC THINKING &EXOTIC METHODS

The beauty of statistics

- Statistics is the science of learning from data.
- The application of statistics to medicine and epidemiology has led to many success stories:
  - Smoking and lung cancer
  - Lipids and coronary artery disease
  - Hormone replacement therapy and breast and uterine cancer
  - Male circumcision and HIV
  - Breast feeding and perinatal HIV transmission
  - Sudden infant death (SID) syndrome
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Identifying the environmental causes of disease, Academy of Medical Sciences Report, 2007.

The ugly side of statistics

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Reheated spaghetti bolognese 'prevents cancer'

By DAILY MAIL REPORTER
UPDATED: 09:38, 21 August 2008

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Eating reheated spaghetti bolognese could reduce your risk of cancer.

Scientists have discovered that multiple rounds of heating - plus a little extra oil - enhance the health benefits of processed tomatoes.

The technique alters the structure of the tomato molecule lycopene so that it is more easily transported into the bloodstream.

Lycopene, a powerful antioxidant, has been shown to prevent cancers and may also combat heart disease and diabetes.

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Why pizza can fight cancer

Pizza has always been seen as a meal high in fat and big guilt factor.

But, according to a study, it can also cut your risk of developing a range of cancers.

Researchers discovered that those who ate pizza at least twice a week were 59 per cent less likely to develop cancer of the oesophagus, had a 34 per cent lower risk of throat cancer and were 26 per cent less likely to get colon cancer.

There is growing evidence of the health benefits of a diet rich in tomato sauce, but this is the first time that experts have claimed eating pizza can fight disease.

Dr Silvano Gallus, of the Mario Negri Institute for Pharmaceutical Research in Milan, said: 'We knew that the tomatoes used in the sauce are considered to be a food that prevents certain tumours.

'However, we did not expect that pizza as a whole offered such high prevention against cancer.' The study involved 3,315 patients with tumours of the digestive system who were compared to almost 5,000 people suffering other ailments.

Each patient had to fill in a questionnaire about their eating habits, including a question on how often they ate pizza, says a report in the International Journal of Cancer.

The amount they ate was not specified but the scientists concluded that regular consumption of pizza helped stave off cancer.

Almost all pizzas contain tomato sauce or puree and this is already proven to have cancerfightingproperties. The secret lies in lycopene, an antioxidant in the skin of tomatoes which makes them red.

It is thought that lycopene may inhibit or even reverse the growth of tumours.

Hygienic thinking and exotic (& native) methods

- Two of the keys to the success stories are:
  (a) The research question was clearly formulated;
  (b) Rigorous statistical analyses were sensibly applied.
- I will refer to (a) as hygienic thinking.
- Because most real life problems have non-standard features, their solution often requires new methods: 'exotic' comes in (b).

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Focus on (a) and (b) with highlights from three examples.

Outline

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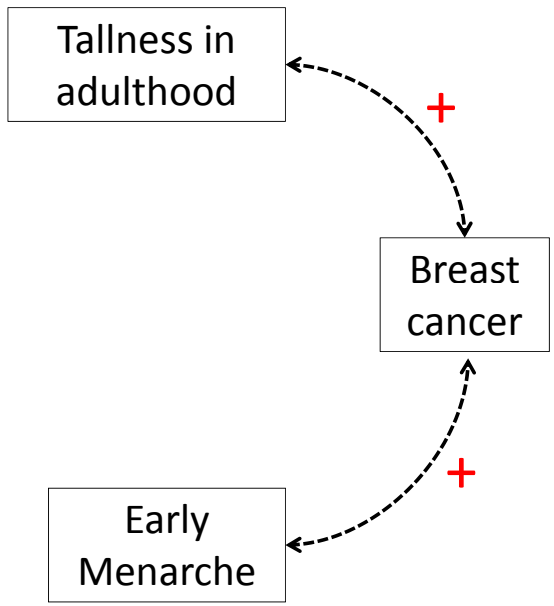
Childhood growth and breast cancer incidence

Collaboration with Isabel dos Santos Silva (LSHTM) and Rebecca Hardy & Di Kuh (UCL)

- Tallness in adulthood and early age at menarche: established risk factors for female breast cancer.



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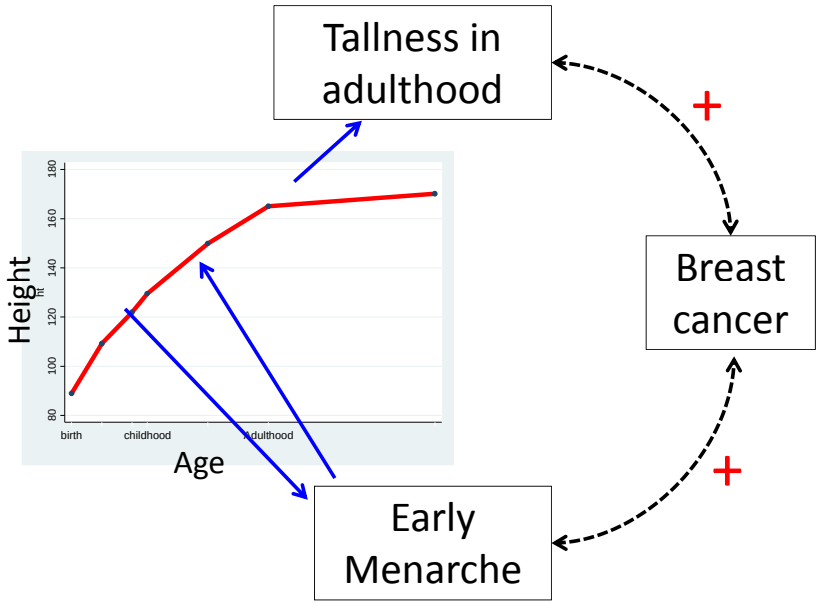

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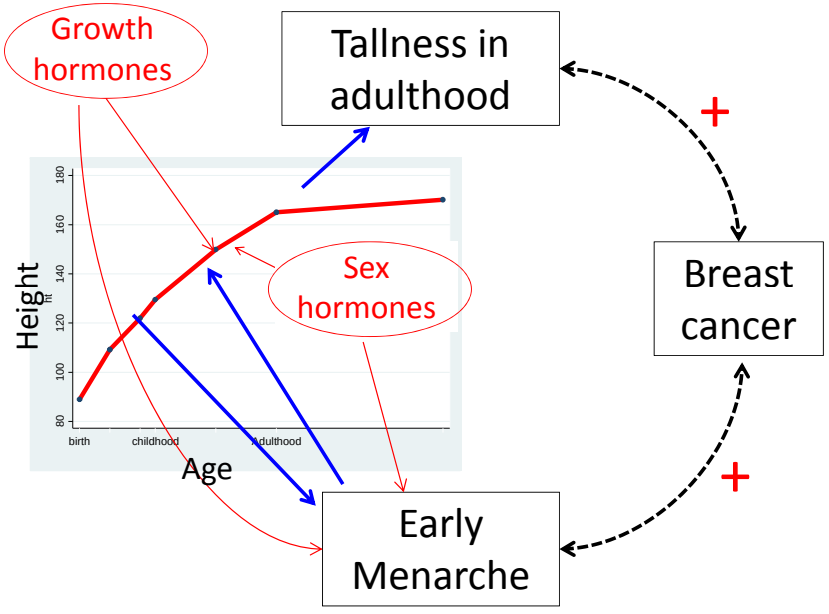

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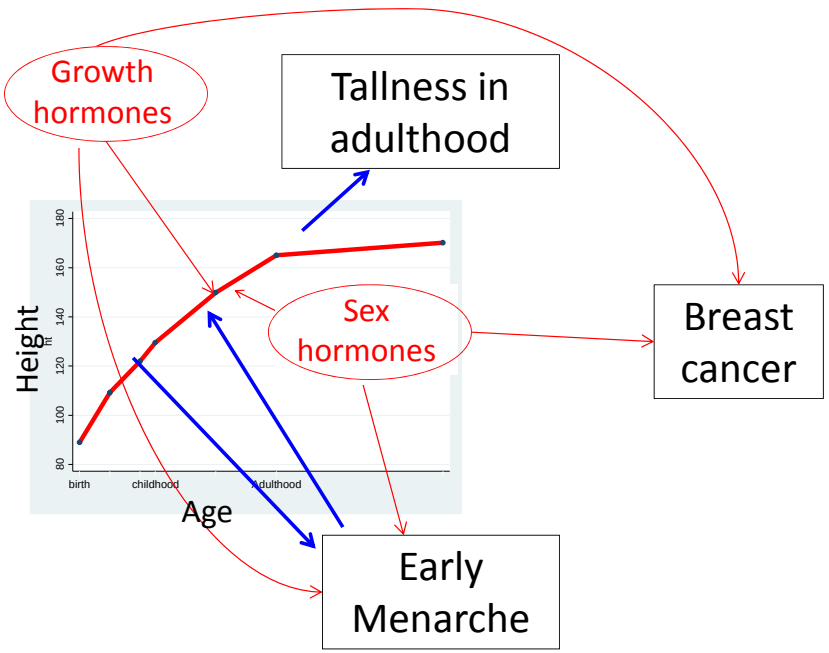

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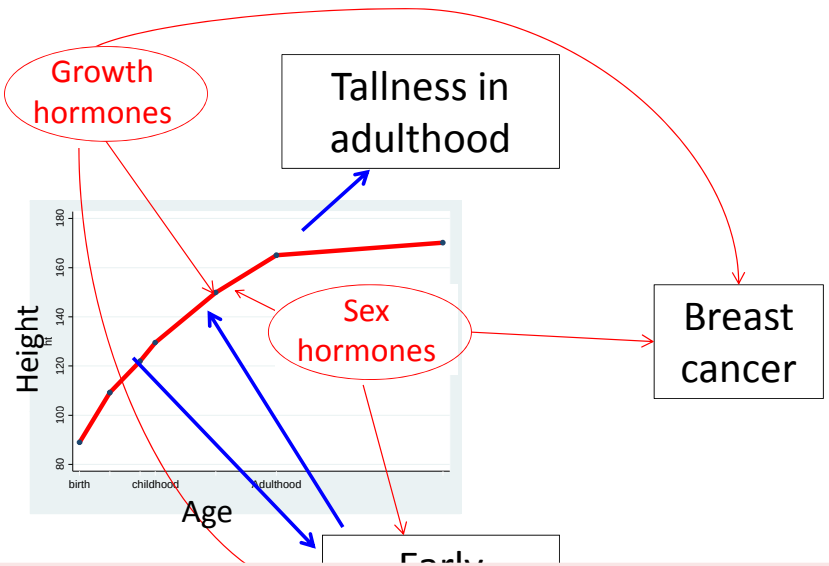

Which features of growth are associated with breast cancer?

Data

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Data:

- ∼2,200 women with linkage to NHS Cancer Register.
- Repeated height measurements at ages 2, 4, 6, 7, 11, 15 years.
- Measurements are however affected by missingness: with only 50% of women having complete childhood height data.

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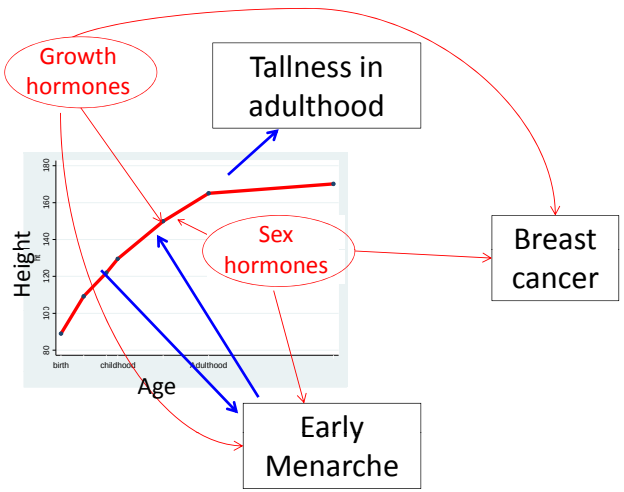

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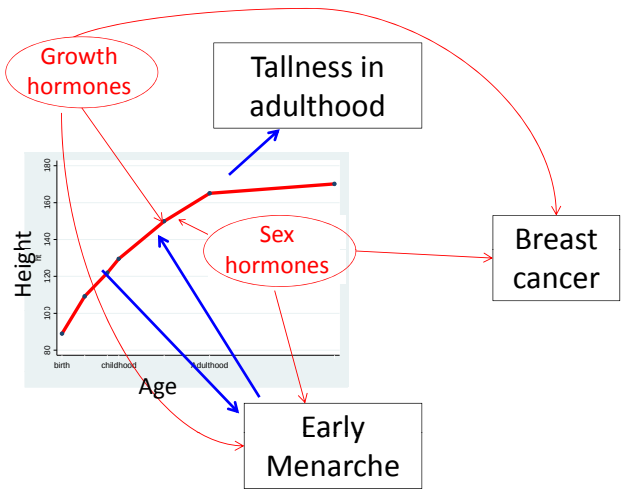

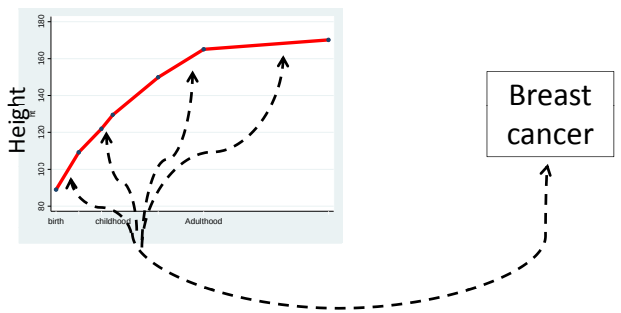

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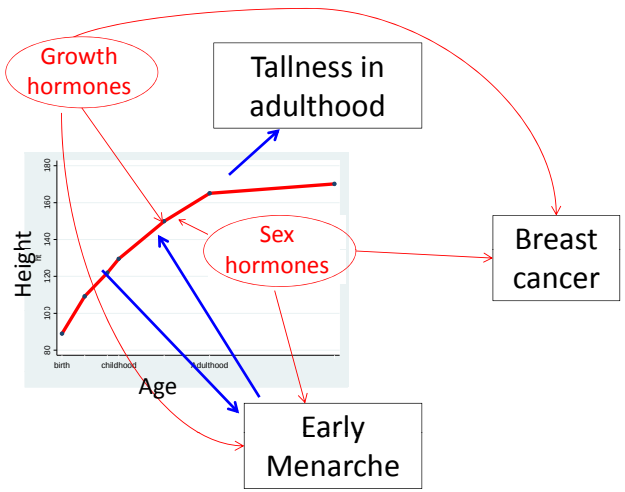

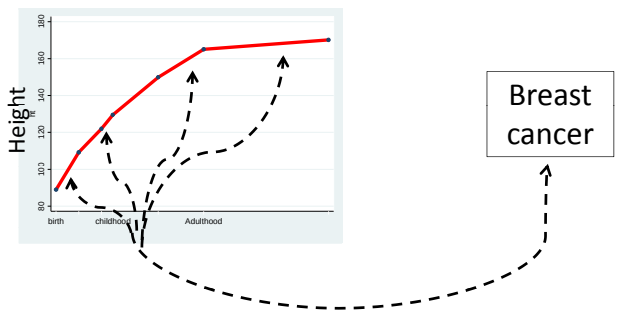

Modelling growth data in relation to breast cancer incidence requires some thinking . . . hence a brief detour.

Modelling growth data in relation to a later outcome

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(i) include all Zs in the same regression model for Y[1]:

$$g\{E(Y|\mathbf{Z})\} = \beta_0 + \beta_1 Z(t_1) + \beta_2 Z(t_2) + \cdots + \beta_K Z(t_K)$$

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(ii) include the first value (size) and then all the subsequent changes:

$$g\{E(Y|\mathbf{Z})\} = \alpha_0 + \alpha_1 Z(t_1) + \alpha_2\{Z(t_2) - Z(t_1)\} + \cdots + \alpha_K\{Z(t_K) - Z(t_{K-1})\}$$

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(ii) . . . or the first value (size) and all subsequent velocities

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Understanding the relations among these specifications is crucial to avoid misinterpreting the results. De Stavola *et al.* , AJE 2006

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Interpretation of specification (i)

Each parameter $\beta_k, k > 0$, in:

$$g\{E(Y|\mathbf{Z})\} = \beta_0 + \beta_1 Z(t_1) + \beta_2 Z(t_2) + \cdots + \beta_K Z(t_K)$$

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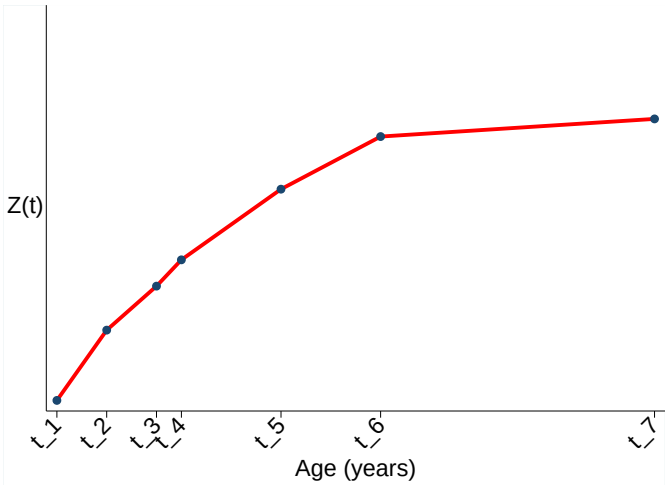

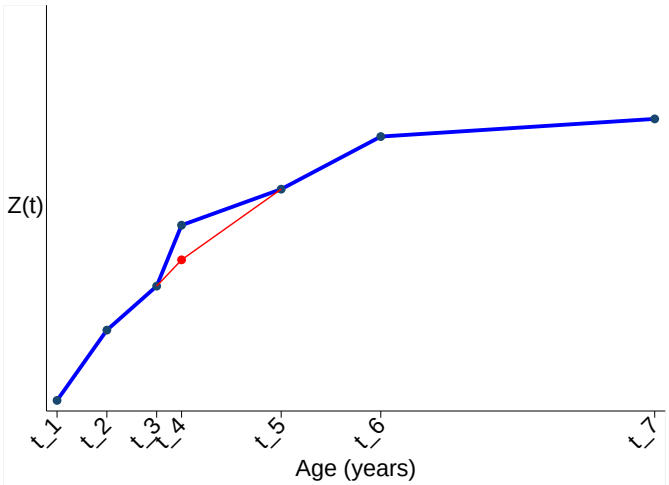

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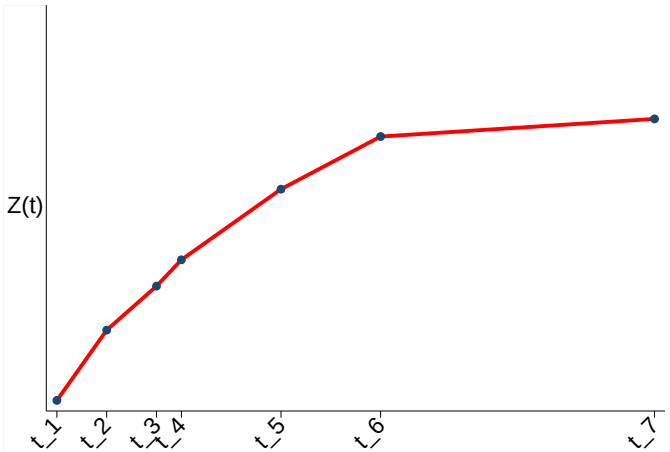

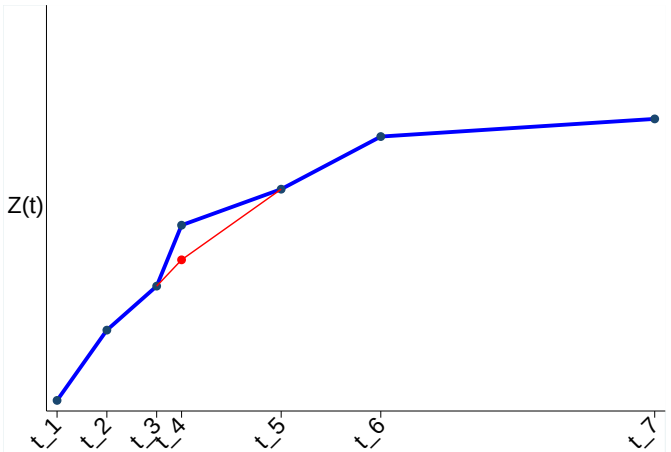

β_k captures the effect of a temporary change in $Z(t)$ that happened in the k-th interval.

Interpretation of specification (ii)

Each parameter $\gamma_k, k > 1$ in:

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represents the the effect on Y of a unit increase in the velocity in $Z(t)$ during the kth interval, *holding all other variables constant*.

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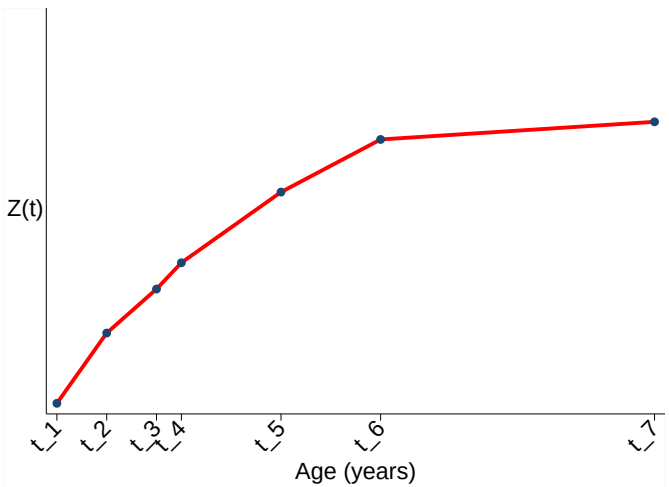

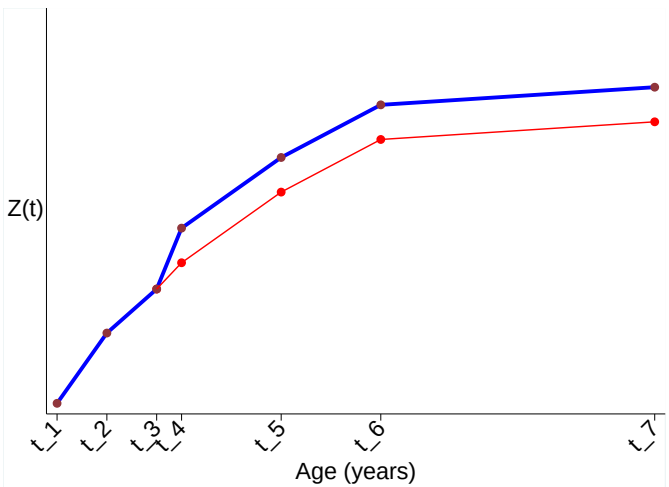

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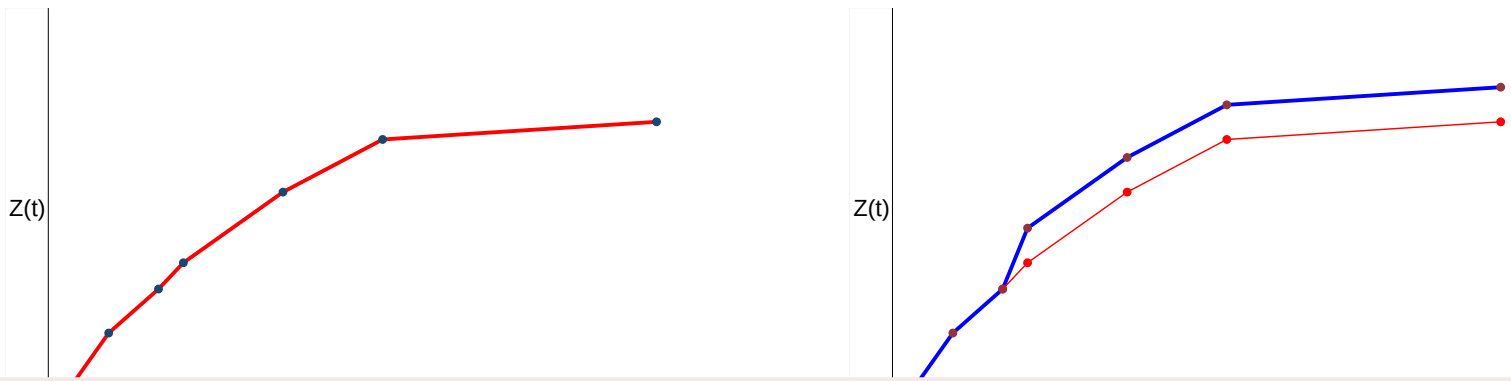
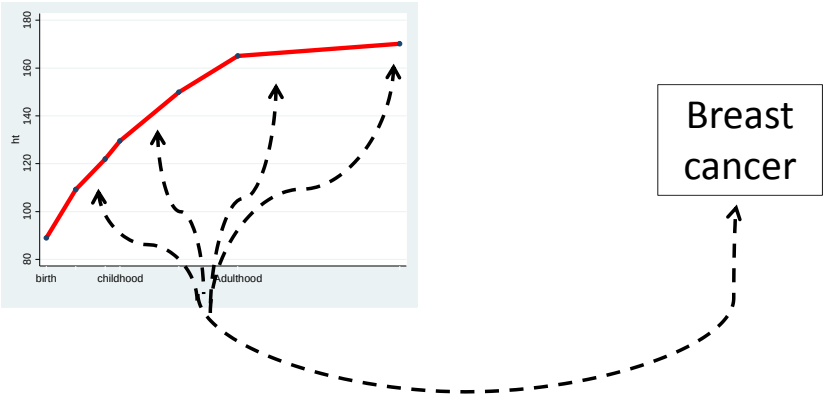


γ_k captures the cumulative effect of a permanent change in $Z(t)$ that happened in the k-th interval.

The question

Which features of growth are associated with breast cancer?



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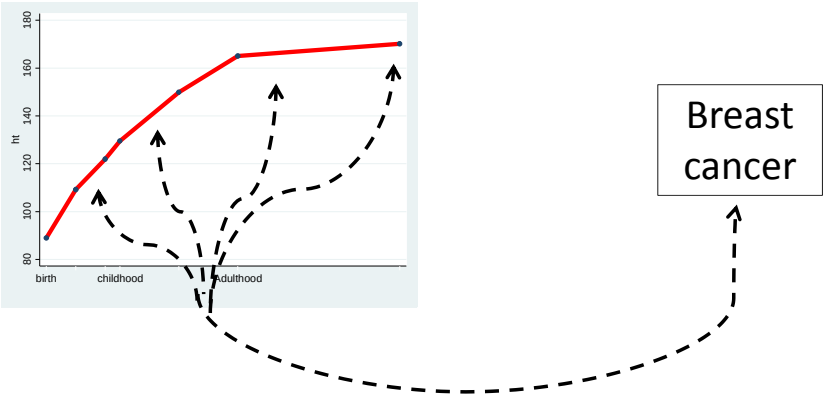

- Two approaches are alternative specifications of the same model[2].
- They differ in terms of the comparisons they make.

[2] Parameters are linear functions of one another: $\gamma_k = \left(\sum_{j=k}^{K} \beta_j\right) / \left(t_k - t_{k-1}\right)$

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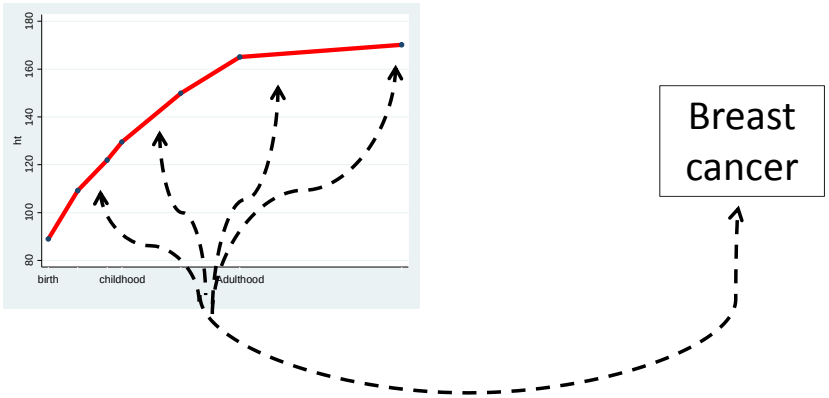

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Specification (ii), *i.e.* in terms of size and velocities, is the most relevant.

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Results

The model:

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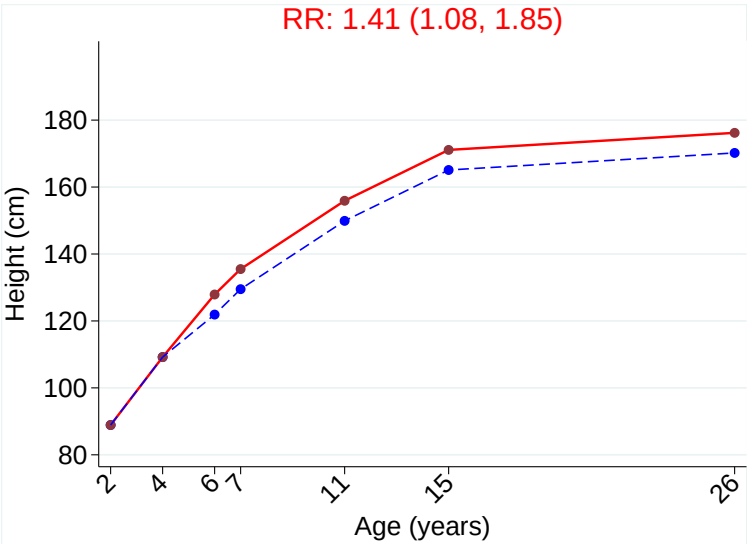

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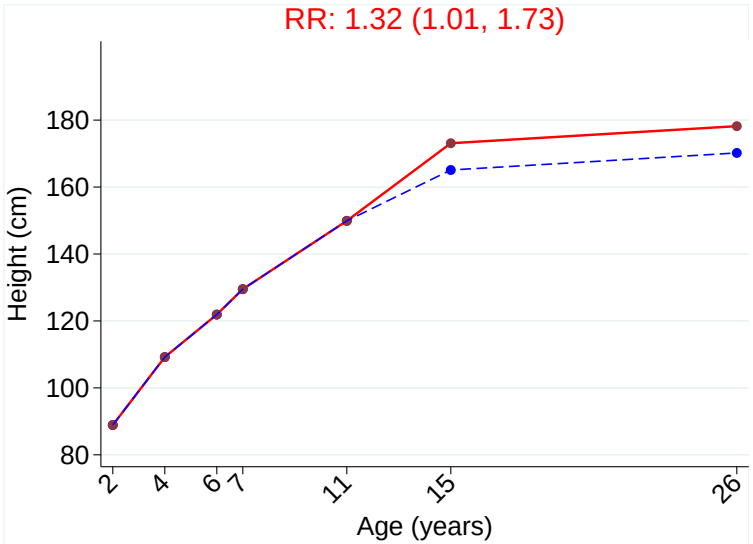

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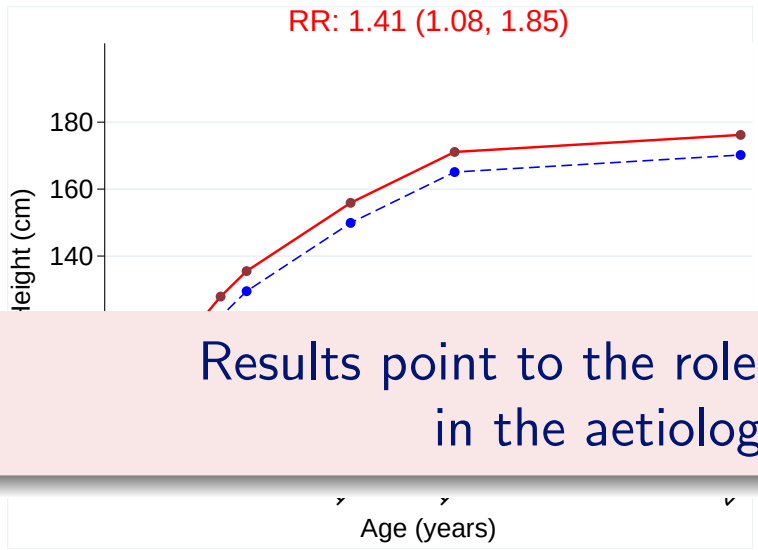
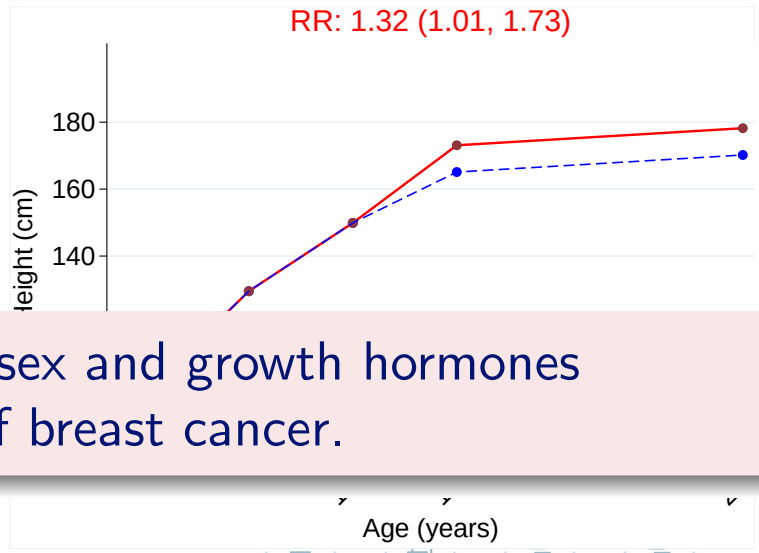


velocity at 11-15y

(rate ratios (RR) *per* cm/year):



Results point to the role of sex and growth hormones in the aetiology of breast cancer.

Addendum

- The paper was submitted to *American Journal of Epidemiology* in 2003.
- Because of missing data, we used (proper) multiple imputation (MI)[3] to reduce selection bias.
- Interestingly, one of our reviewers wrote:

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A neat example of how widely-accepted methods often start as exotic!

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Outline

Intergenerational correlations in size at birth

Collaboration with Dave Leon (LSHTM) and Ilona Koupil (Stockholm Un. & Karolinska Institutet)

- Size at birth has been the focus of extensive research in chronic disease epidemiology in the last 20+ years.
- Strong correlations in size at birth between parents and offspring have been observed in different populations, with those between mothers and offspring consistently found to be stronger ($\sim$20-25%).
- Correlations explained by genetic inheritance but other mechanisms likely to be at play, in particular those linked to continuities in environmental (socio-economic) circumstance.
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Uppsala Birth Cohort Multigenerational Study (UBCoS Multigen):

Ongoing prospective study of men and women born in Uppsala, Sweden (1915-1929) and their descendants.

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Cohort	Generation	Size at birth[4]
⇑	G0	
Original	G1	✓
⇓	G2	
⇓	G3	✓

G1	G1-G3 Pairs
10,136	28,152

[4] Sex & gestational age standardized birth weight

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(a) *How strong are the G1-G3 correlations in size at birth?*

(b) *Do they vary by maternal/paternal lineage?*

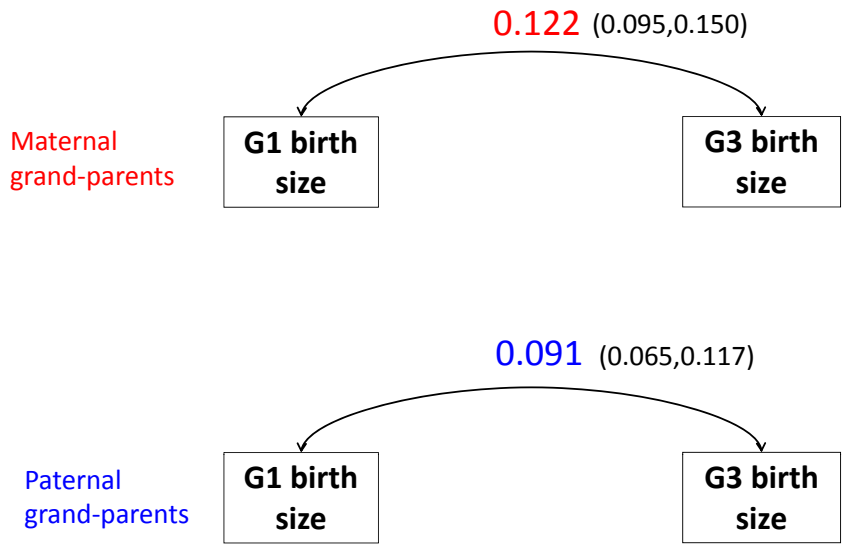
(c) *Can they be explained by socio-economic continuities?*

[4] Sex & gestational age standardized birth weight

Standard analyses (a)

(a) How strong are the G1-G3 correlations in size at birth?

Marginal correlation between sex and gestational age standardized birth weight of G1 and G3:



Standard analyses (b)

(b) Do they vary by maternal/paternal lineage?

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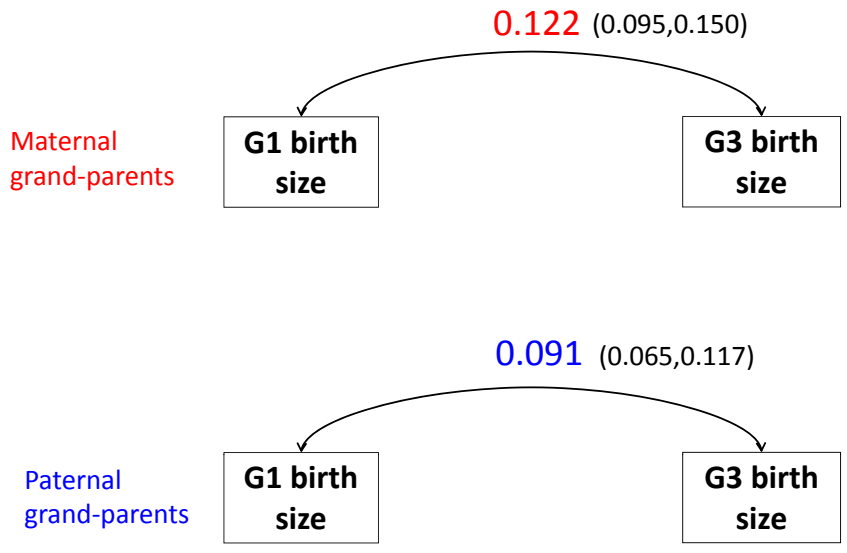

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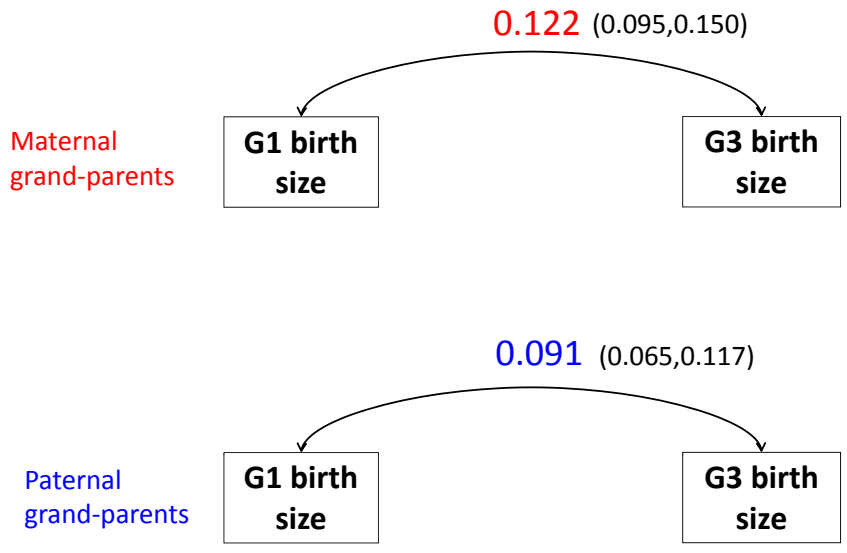

Maternal *vs.* paternal lineage: P=0.02.

Evidence of moderate correlations that differ by lineage.

Standard analyses (c)

(c) Are correlations 'explained' by socio-economic continuities?

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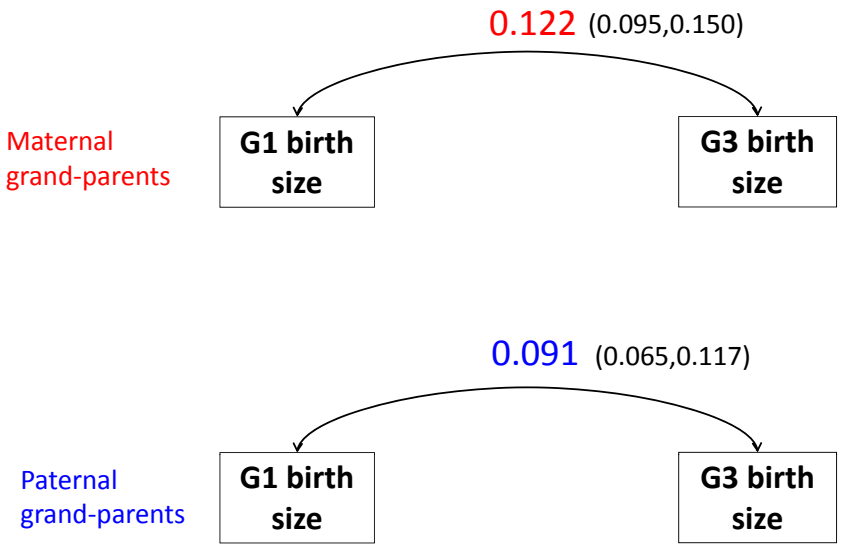

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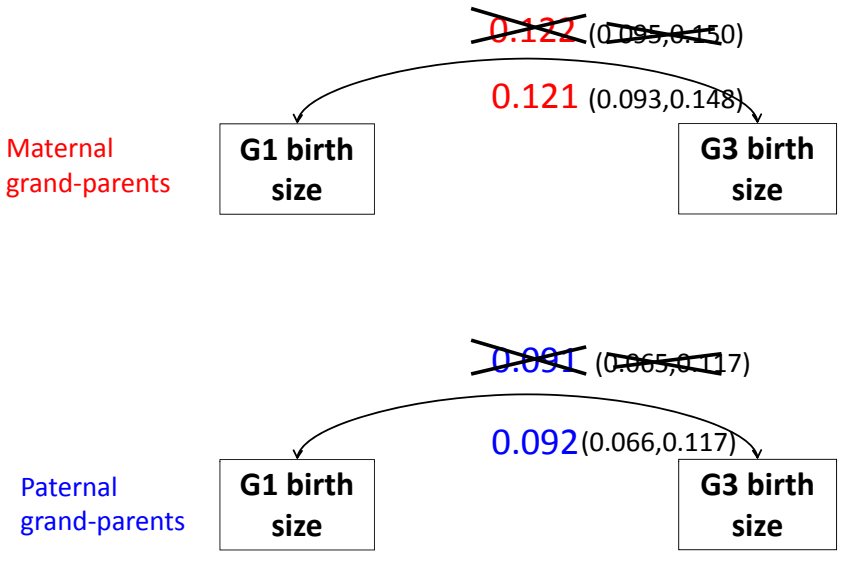
Correlations adjusted for G0-G2 socio-economic factors:



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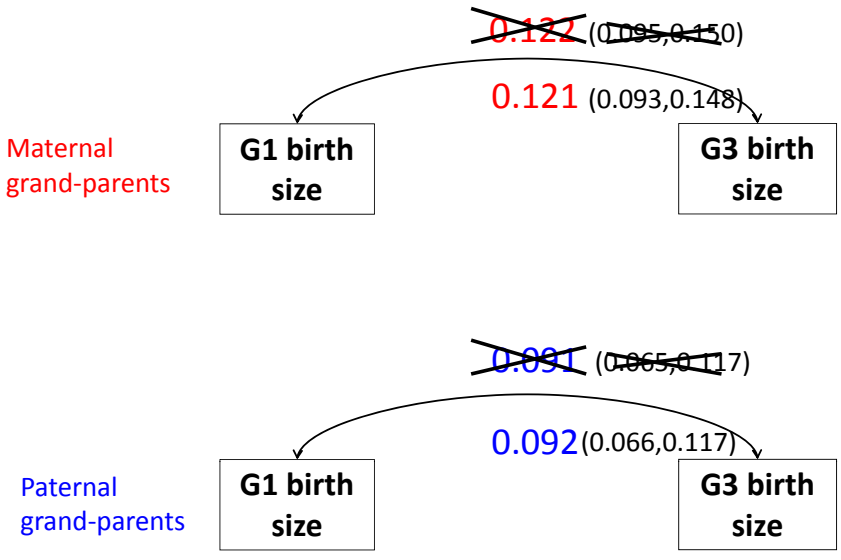

No evidence of role of socio-economic continuities in explaining biological correlations.

Exploiting the data structure: genetic modelling

Apportion components of the correlation to:

- Foetal genes: F_1 for grandparents and F_3 for grandchildren[5].

  They are shared with probability 1/4.

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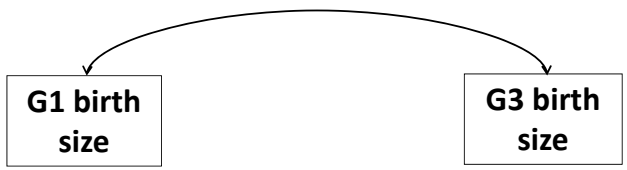
- Shared environment: represented by C. This represents the environmental factors that are maintained from one generation to the next.



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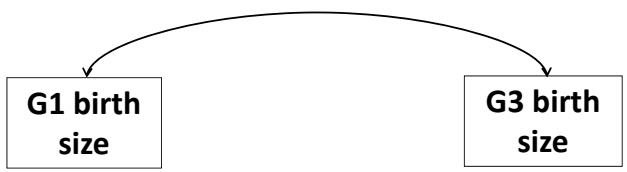

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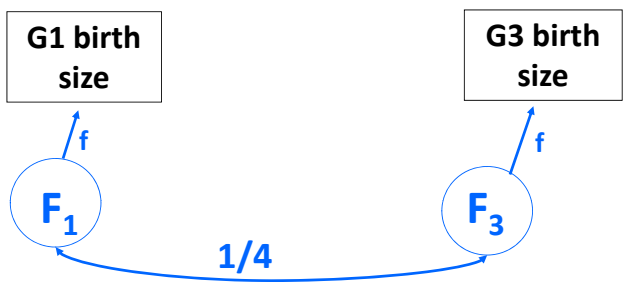

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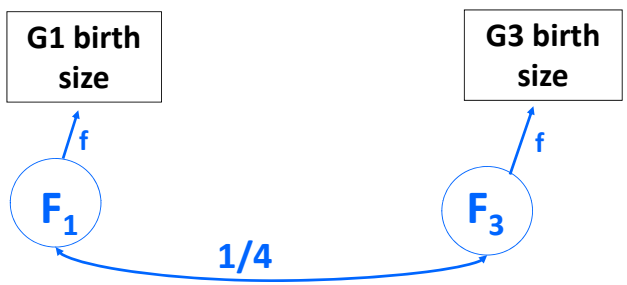

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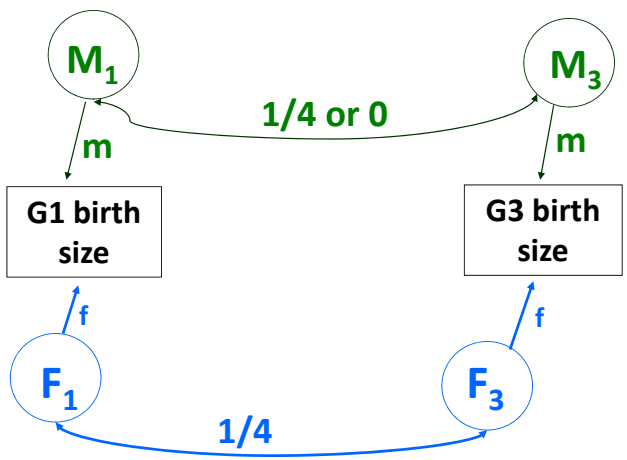

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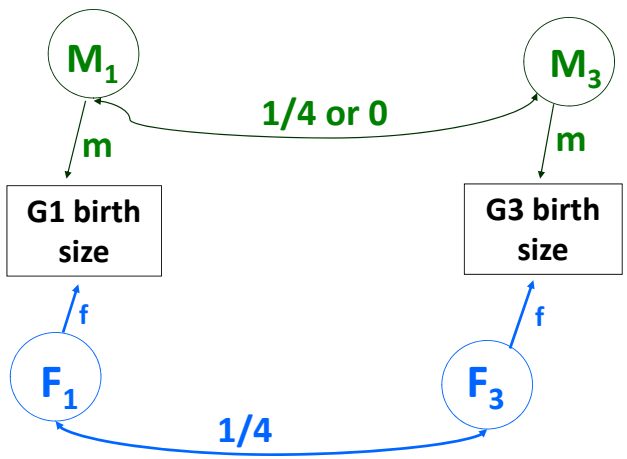

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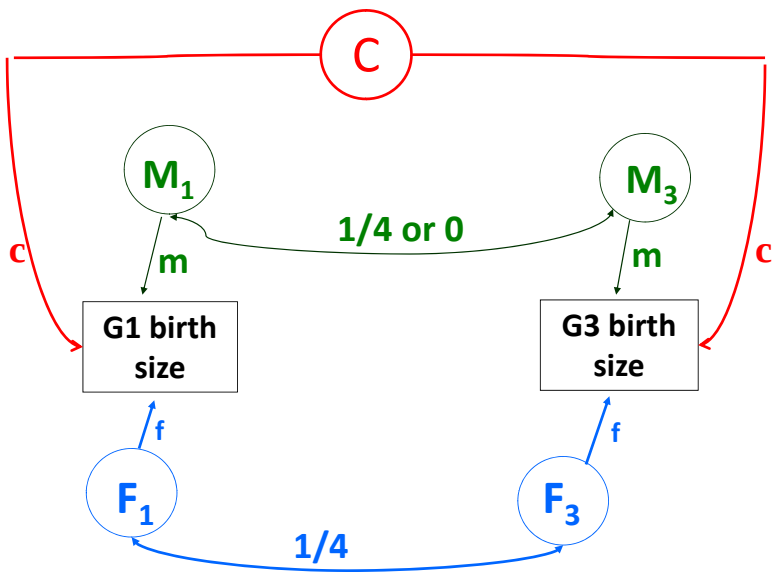

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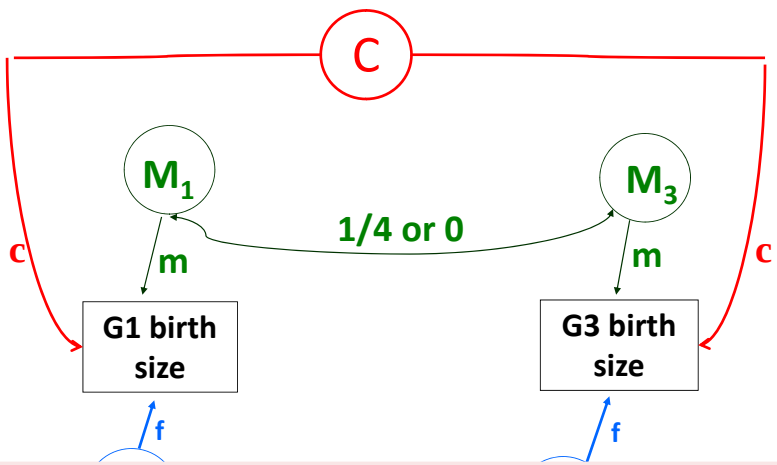

The regression coefficients f, m, c, represent the contribution to the variances.

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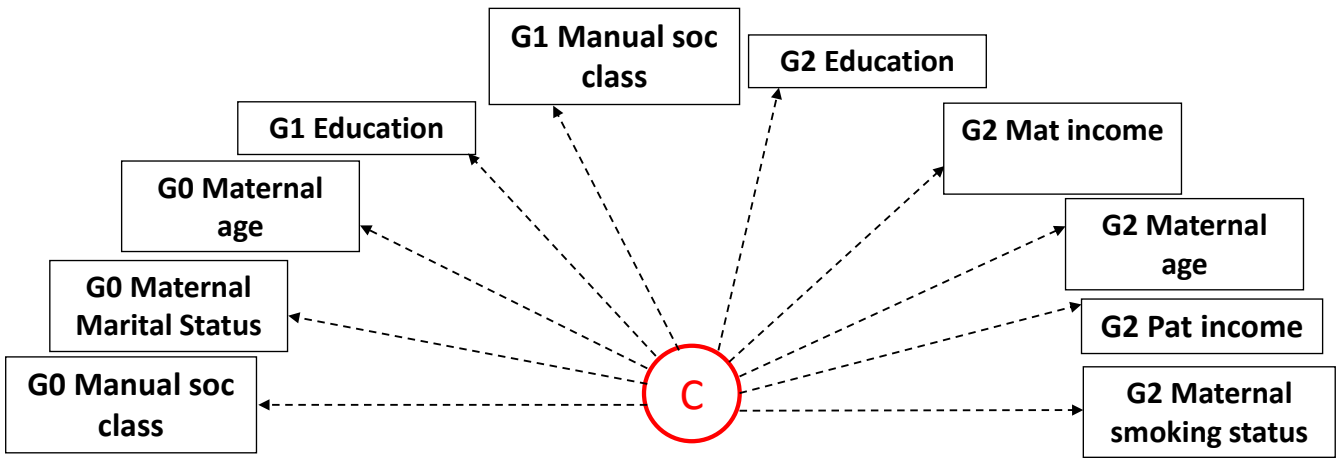
Identification

- None of these components is measured.
- However, assuming that C, the latent shared environment, is manifested by the socio-economic and demographic factors measured for the 3 generations:



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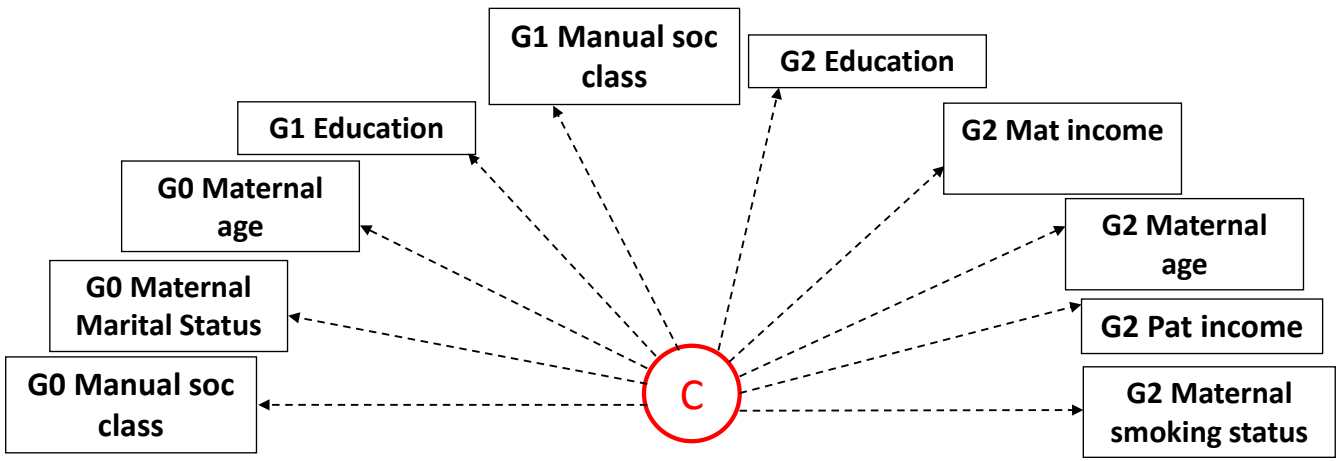

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New results

From the estimates of f, m, c we can partition the contributions to the correlation, separately by grandparental (GP) group.

Estimated percentage of contribution to the intergenerational correlation in standardized size at birth:

	Stand Birth weight	
	Estimate (%)	95% CI
Maternal GP	11.6	5.9, 17.3
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Contribution apportioned to the shared environment is small (about 11-14%). (Results robust to departures from the assumed genetic associations.)

Comments

There are two main reasons for why these results differ from those obtained from simple regression analysis.

The biometric model:

- includes additional information (expected genetic correlations),
- uses the information from SEP/demographic indicators to define a latent shared environment and, in doing so, deals with misclassification error in these variables (under certain assumptions).

Outline

Maternal BMI and eating disorders (ED)

Collaboration with Rhian Daniel (LSHTM), Nadia Micali (UCL), and George Ploubidis (LSHTM)

Eating disorders (ED): abnormal eating habits that may involve either insufficient or excessive food intake.

- Maternal influences are thought to play a role, in particular via own body shape, *e.g.* proxied by body mass index (BMI).

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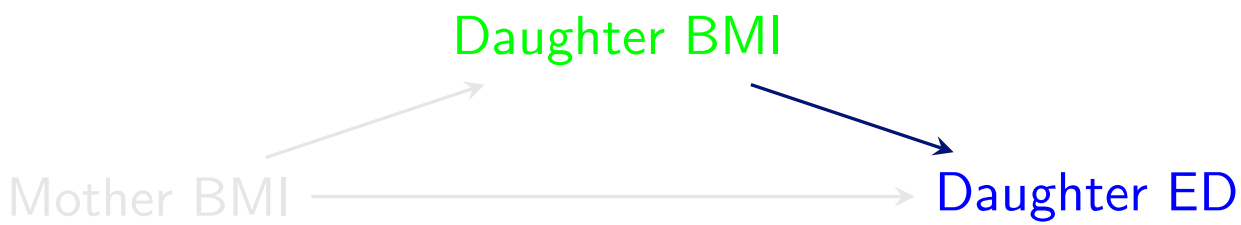

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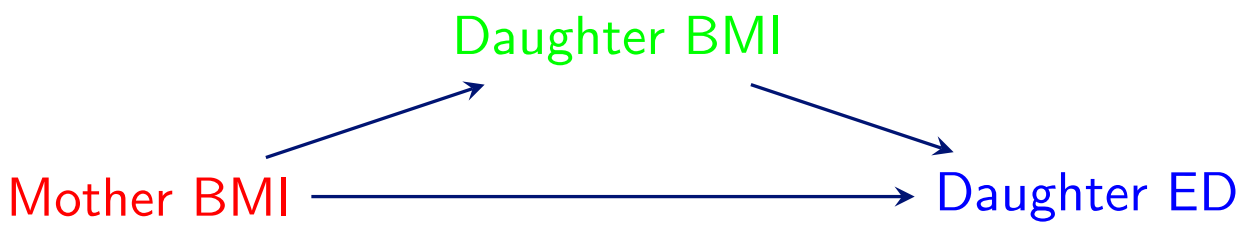

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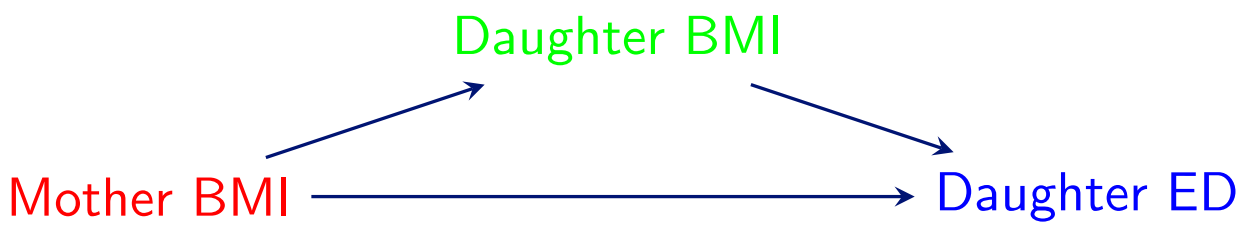

Is the effect of maternal BMI mediated by the daughter's own BMI?

De Stavola *et al.* & Daniel *et al.* (both under revision)

Data

Avon Longitudinal Study of Parents and Children (ALSPAC):

Prospective study of children born in 1991-2.

- Data on various maternal characteristics, including pre-pregnancy body mass index (BMI), and on daughter's birth weight and BMI measured from 7 to 13y.
- Information on ED behaviours collected at age 14y with questions about excessive exercise, binge eating & fasting, summarized via an ED score.

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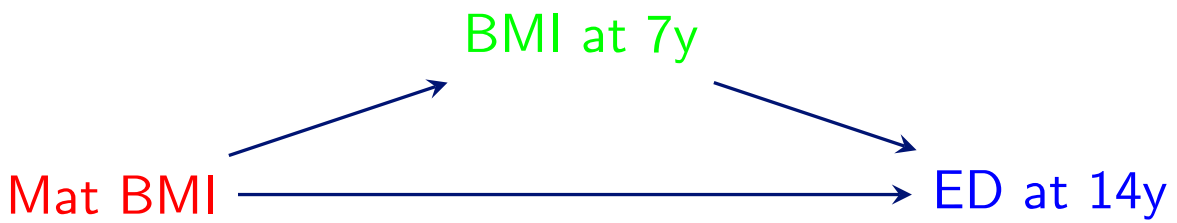

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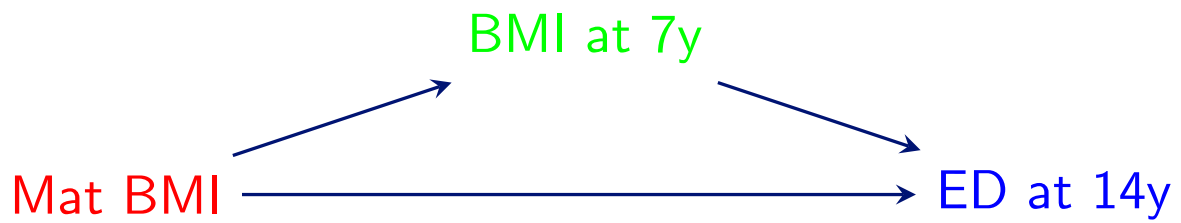

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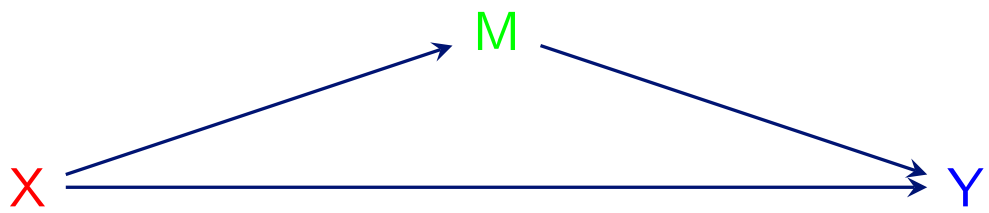

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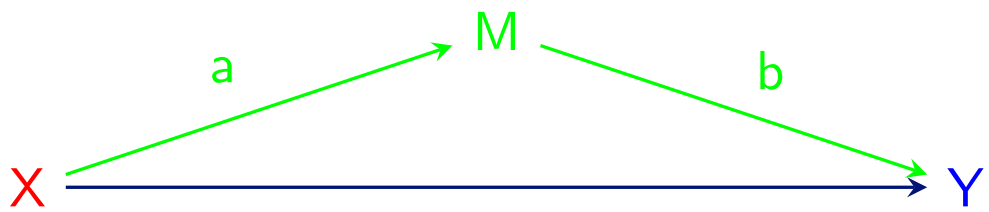

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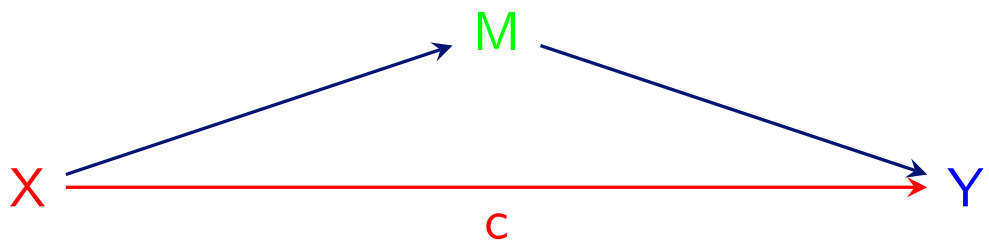
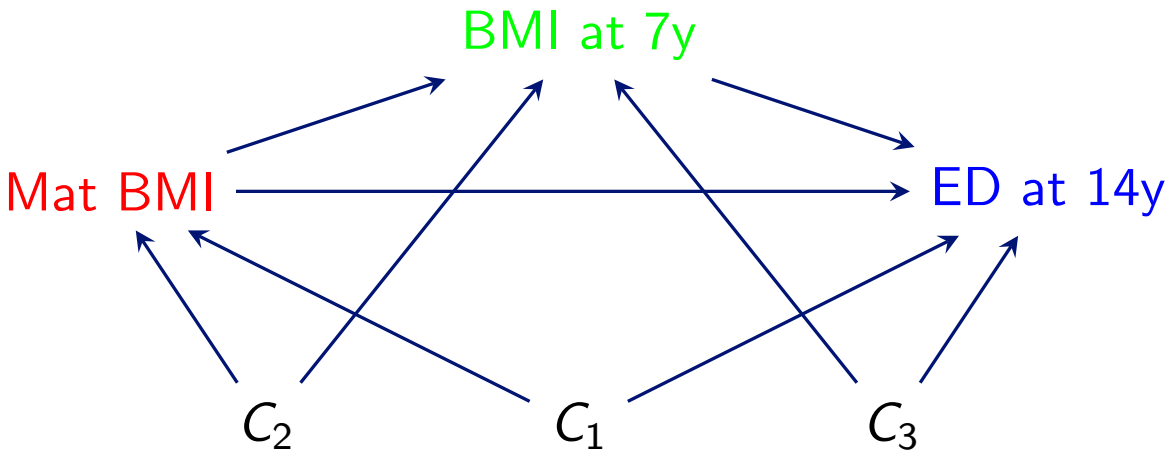
- Long tradition in mediation analysis, starting from Sewall Wright's path analysis.
- Under certain conditions, it allows the decomposition of a total causal effect into one that is transmitted via a mediator M (the 'indirect effect') and one that is not mediated via M (the 'direct effect').



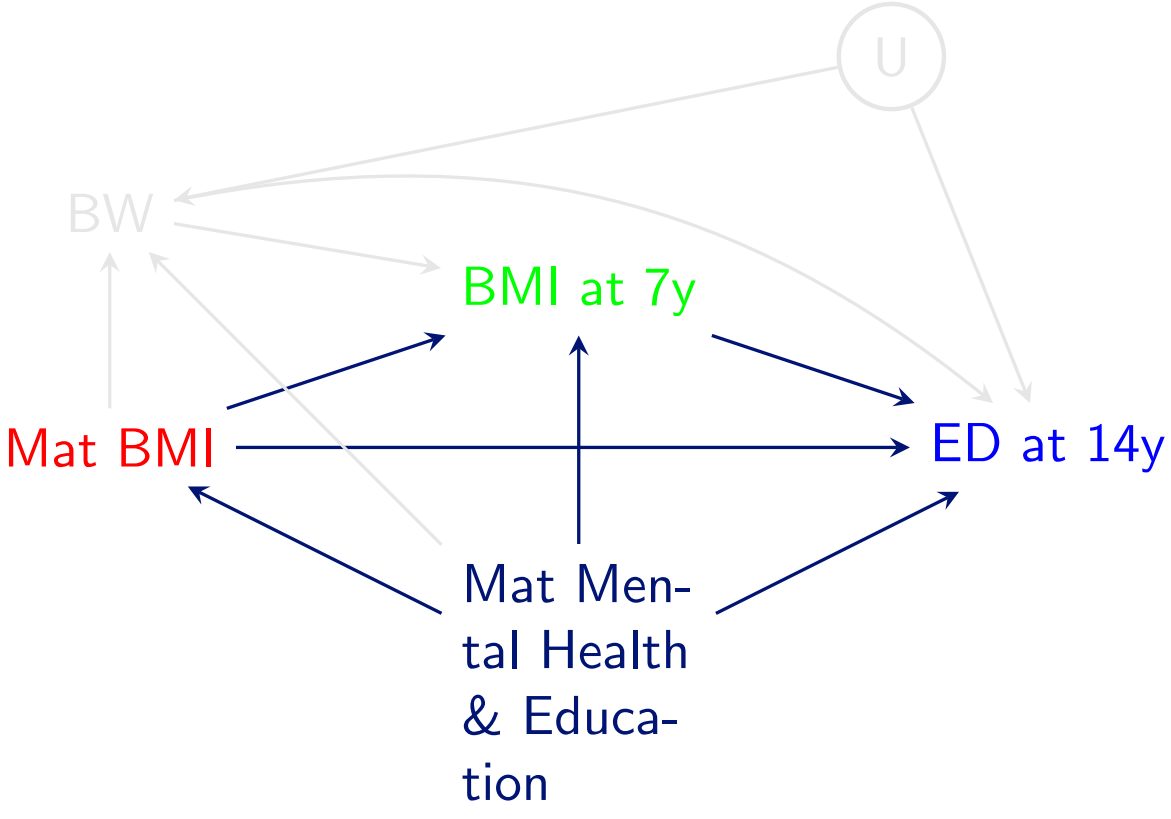
Mediation in practice

- To identify the causal parameters a, b and c, all common causes of X, M and Y should be measured:



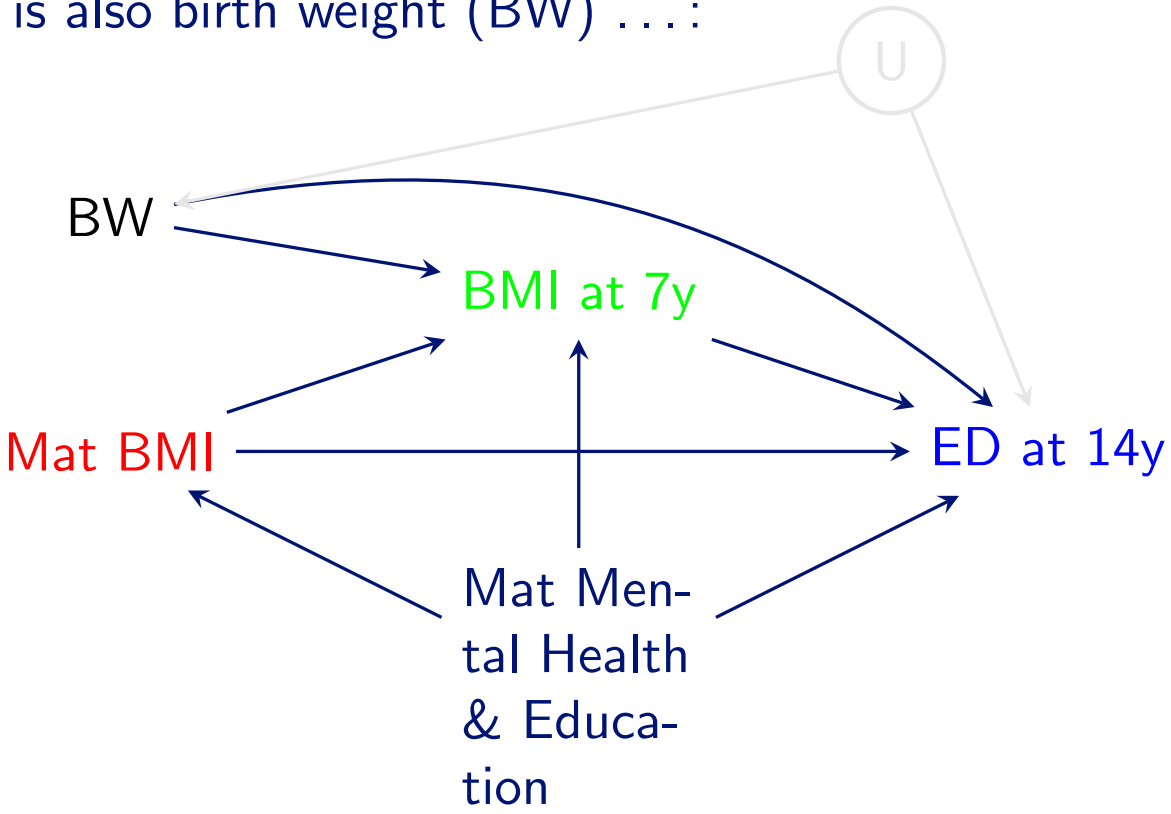
Mediation in practice

- To identify the causal parameters a, b and c all common causes of X, M and Y should be measured. Here maternal mental health and education are measured common causes of X, M and Y:



Mediation in practice

- To identify the causal parameters a, b and c all common causes of X, M and Y should be measured. Here maternal mental health and education are measured common causes of X, M and Y:
- There is also birth weight (BW) . . . :



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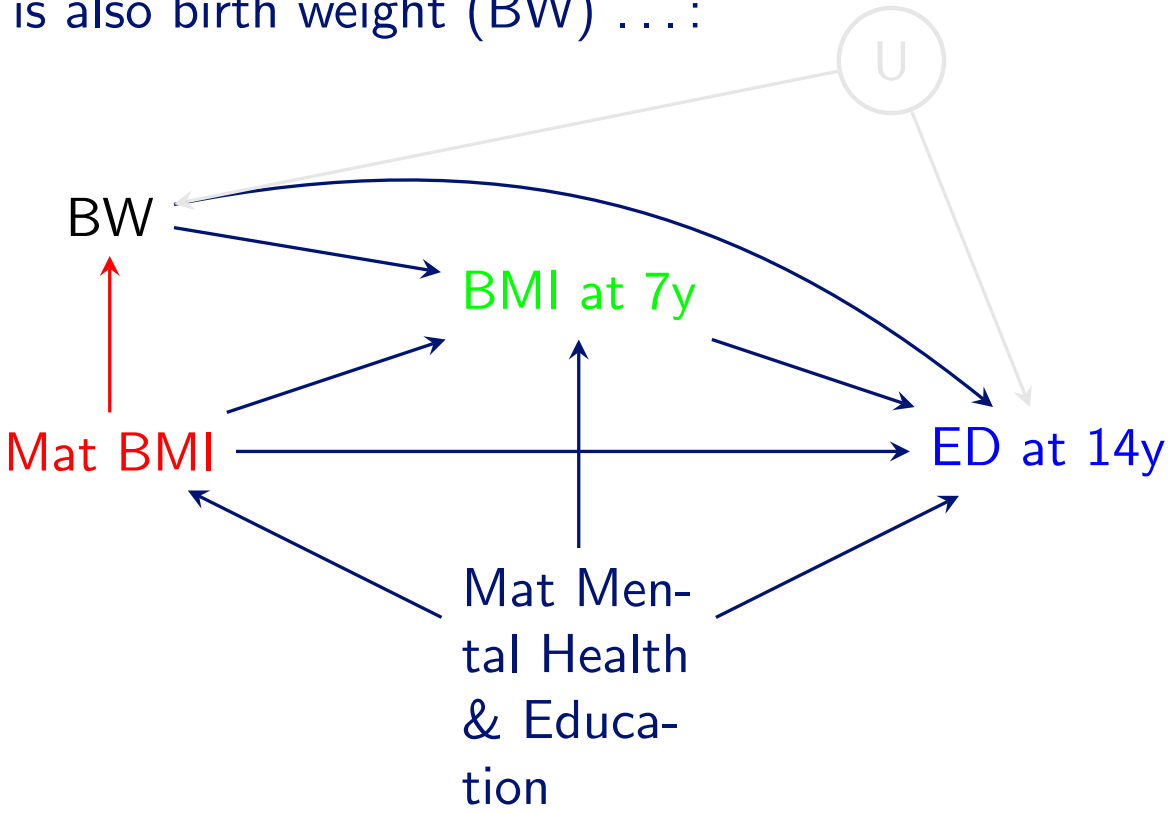

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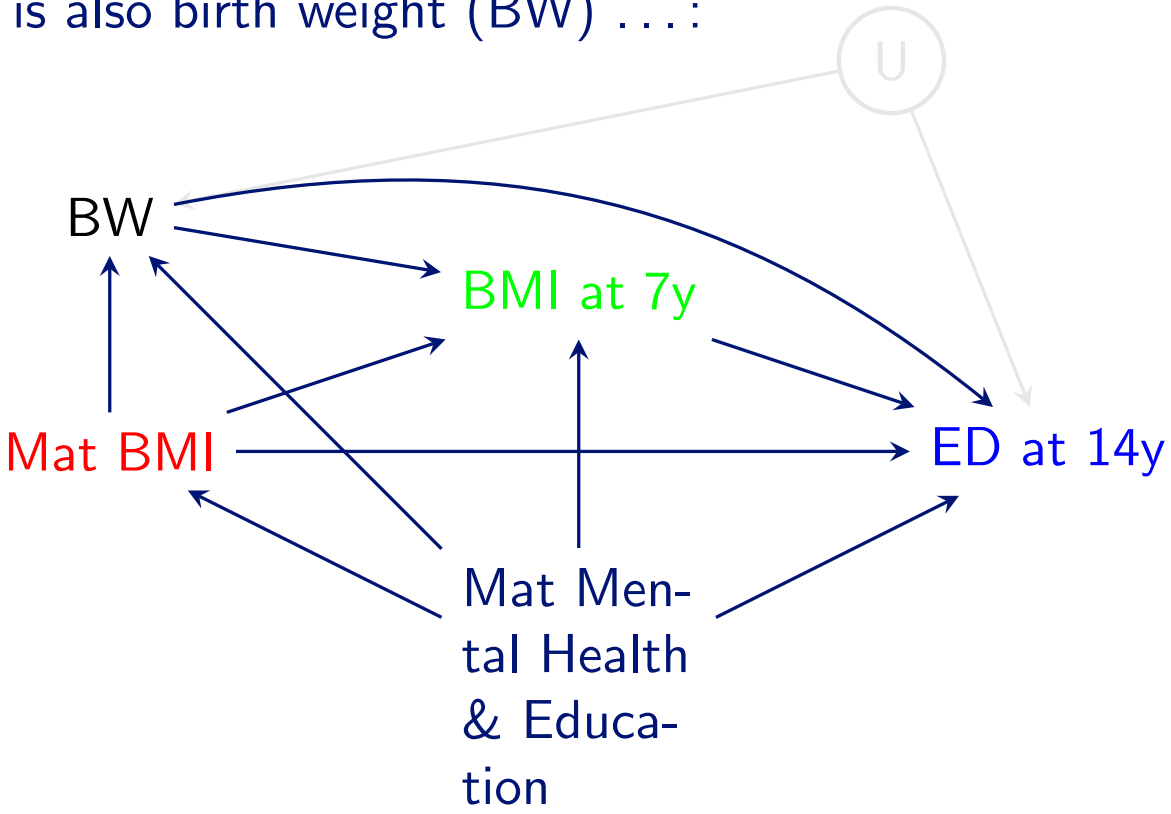

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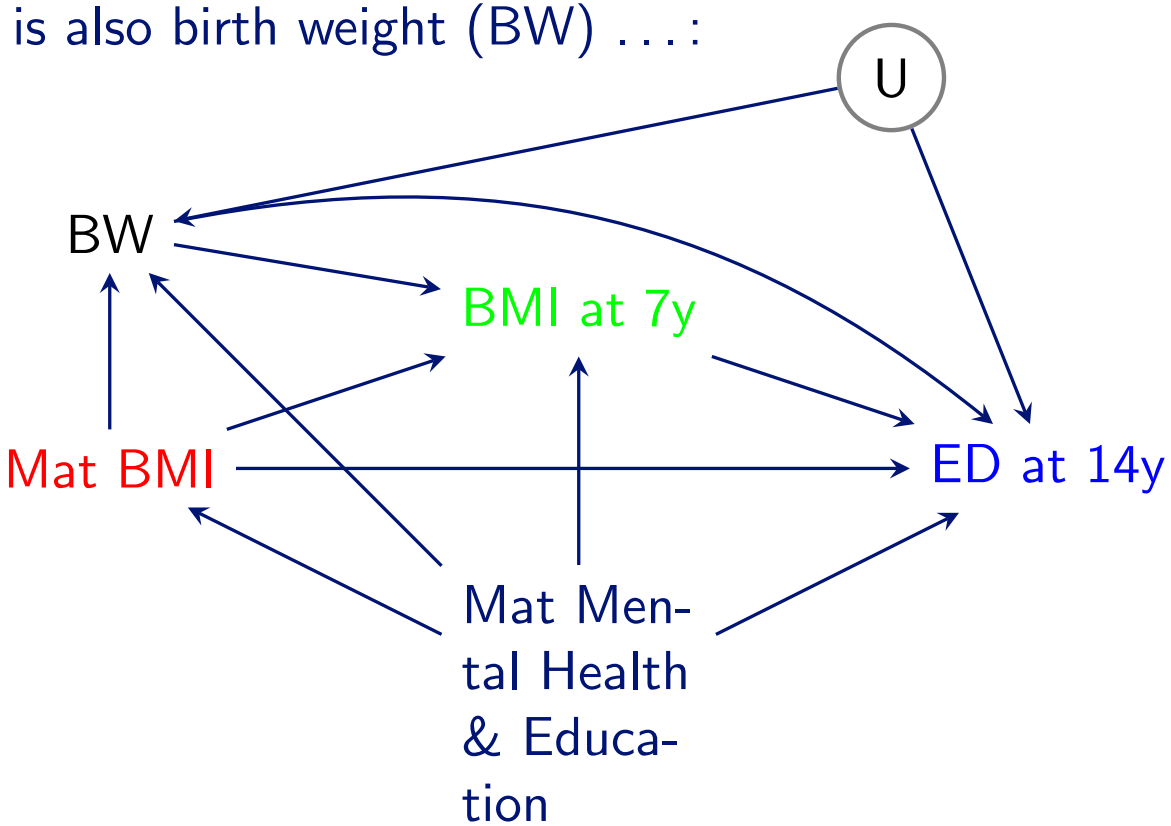

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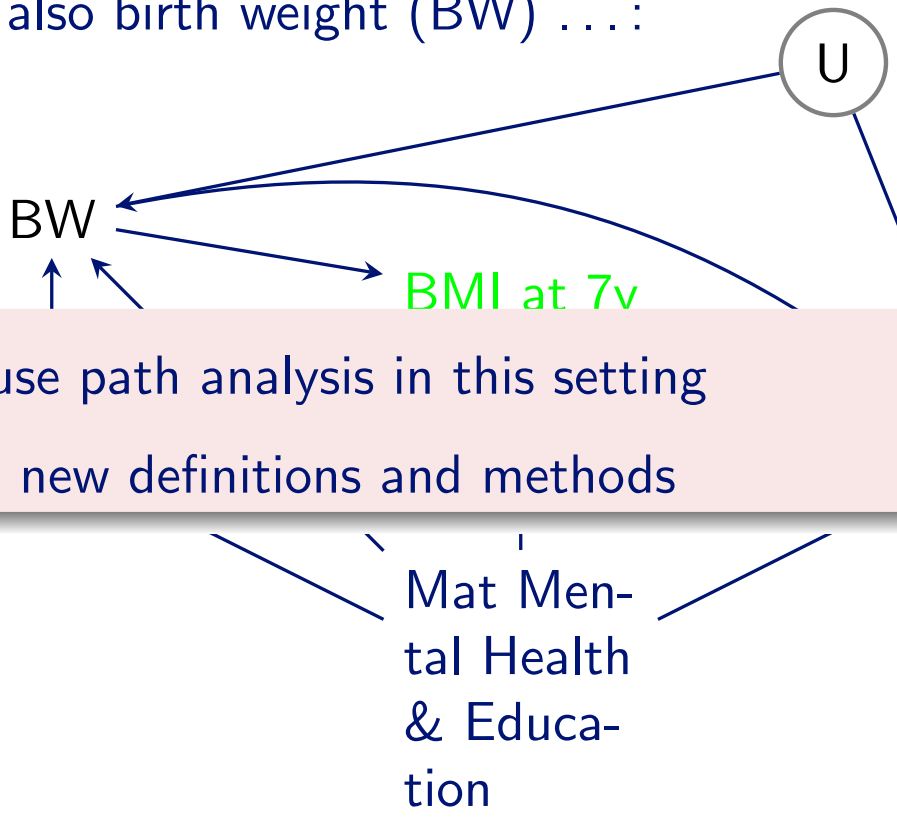
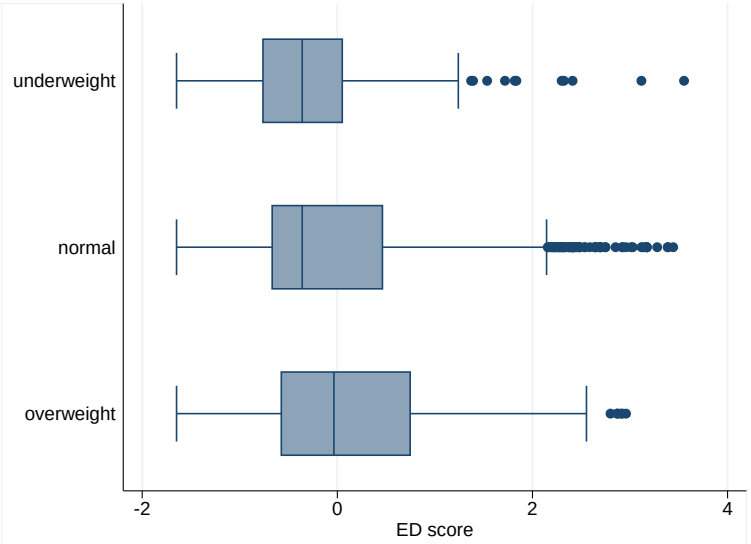


- Cannot use path analysis in this setting
- We need new definitions and methods

Total effect of maternal BMI on daughter's ED score

ED score by maternal BMI



Estimated total effect of maternal BMI on ED score (mean differences)

Maternal BMI	$\hat{\beta}$	(SE)
Underweight	–0.08	(0.09)
Normal	0	-
Overweight	0.22	(0.05)

Controlled for Mat education and mental health disorders

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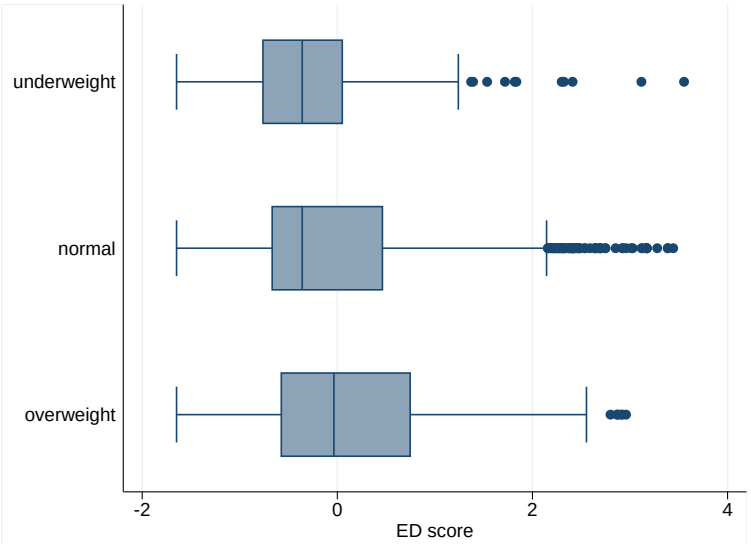

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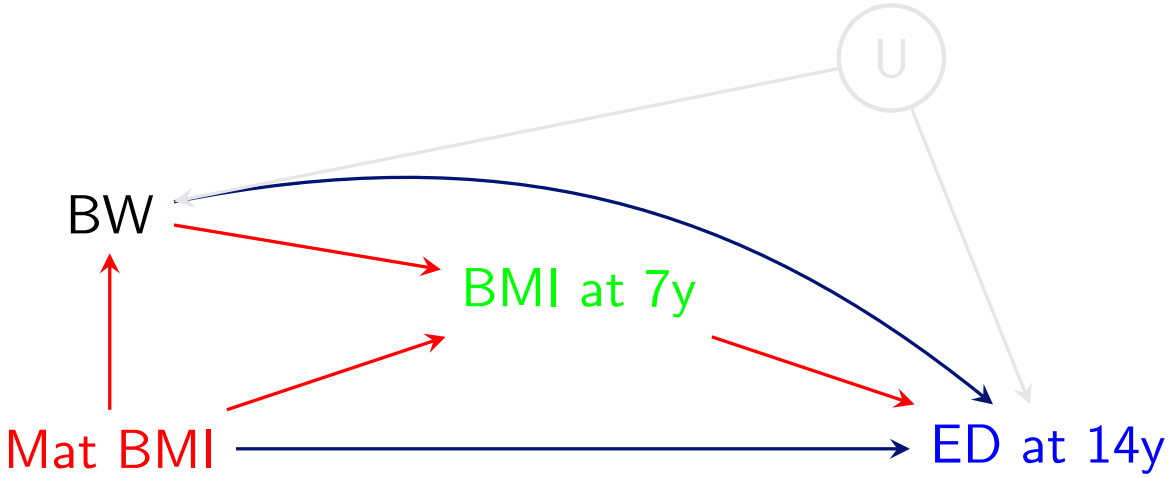
- Harmful effect of maternal overweight
- No evidence of effect of maternal underweight

Decomposition of effects

Effect* of Mat BMI mediated via daughter's childhood BMI at 7y:

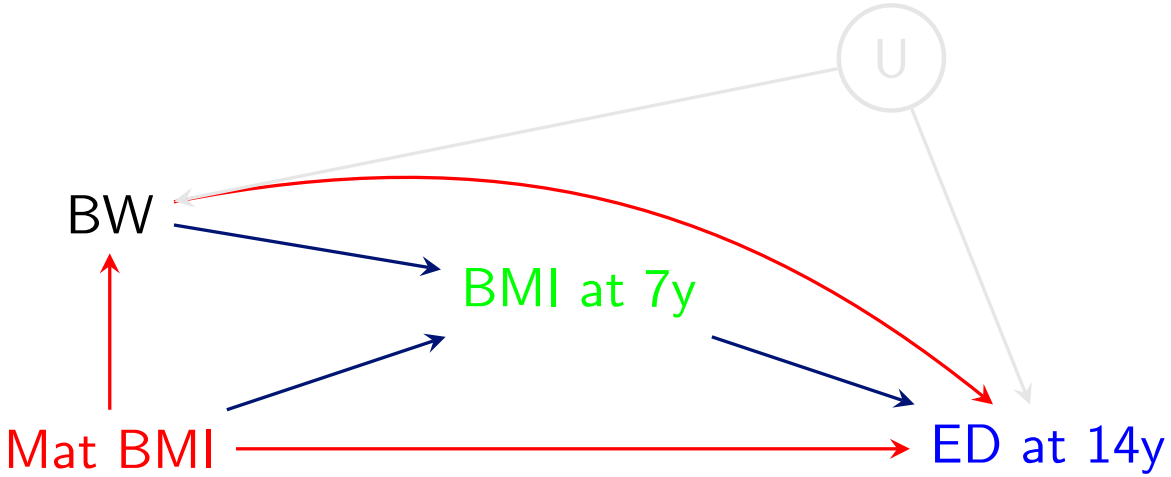


Maternal BMI	Mediated		Not mediated		**Total**	
	$\hat{\beta}$	(SE)	$\hat{\beta}$	(SE)	$\hat{\beta}$	(SE)
Underweight	–0.23	(0.03)	0.15	(0.09)	**–0.08**	(0.09)
Normal	0	–	0	–	0	–
Overweight	0.15	(0.02)	0.07	(0.06)	**0.22**	(0.05)

* Estimated via g-computation.

Decomposition of effects

Effect* of Mat BMI not mediated via daughter's childhood BMI at 7y:



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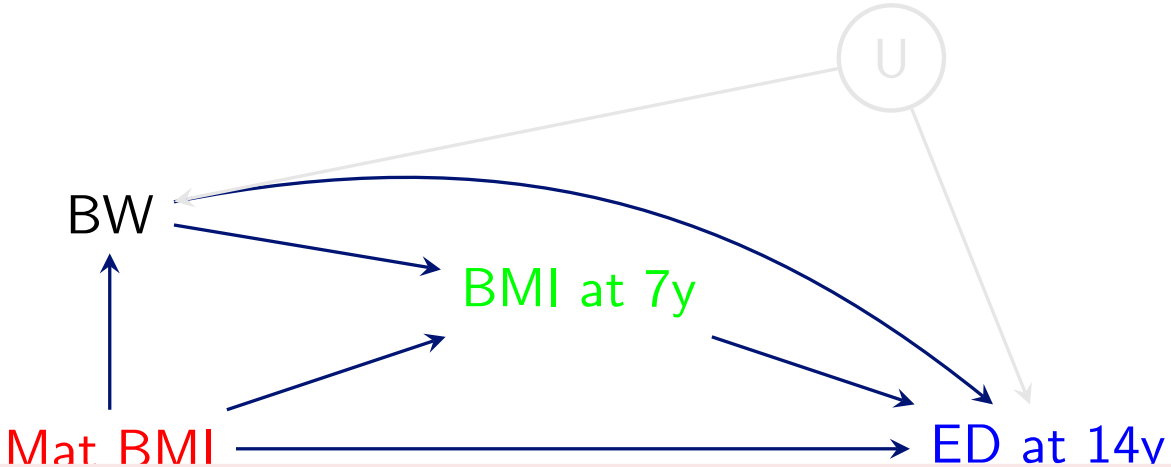

- Most of the harmful effect of overweight in mothers is mediated by childhood BMI.
- Underweight in mothers has instead opposite direct and indirect effects that seem to cancel each other.

Normal	0	–	0	–	0	–
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More complex mediating effects

Consider an additional mediator of interest: BMI velocity in childhood

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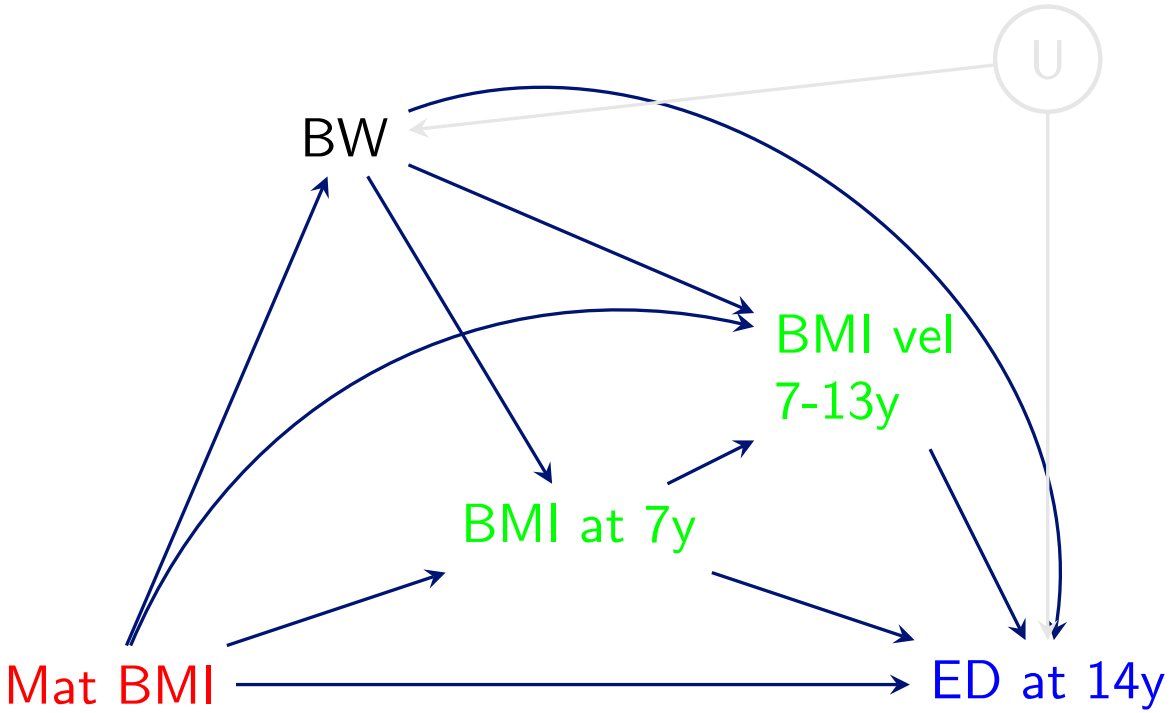

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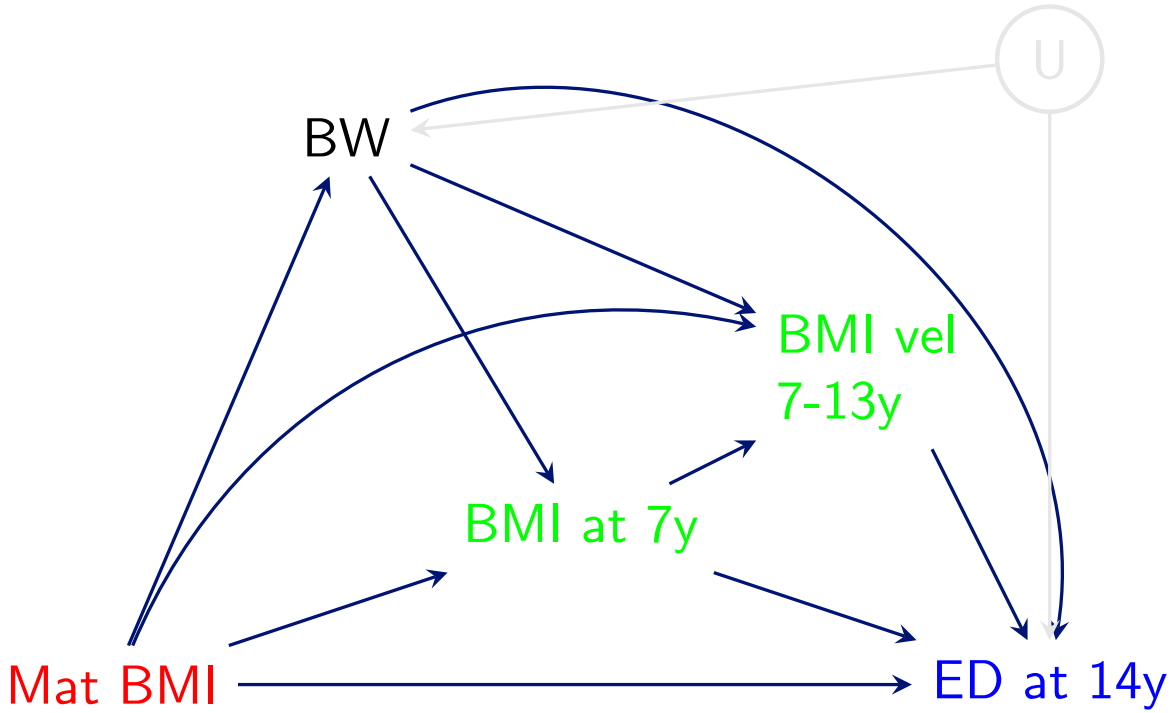
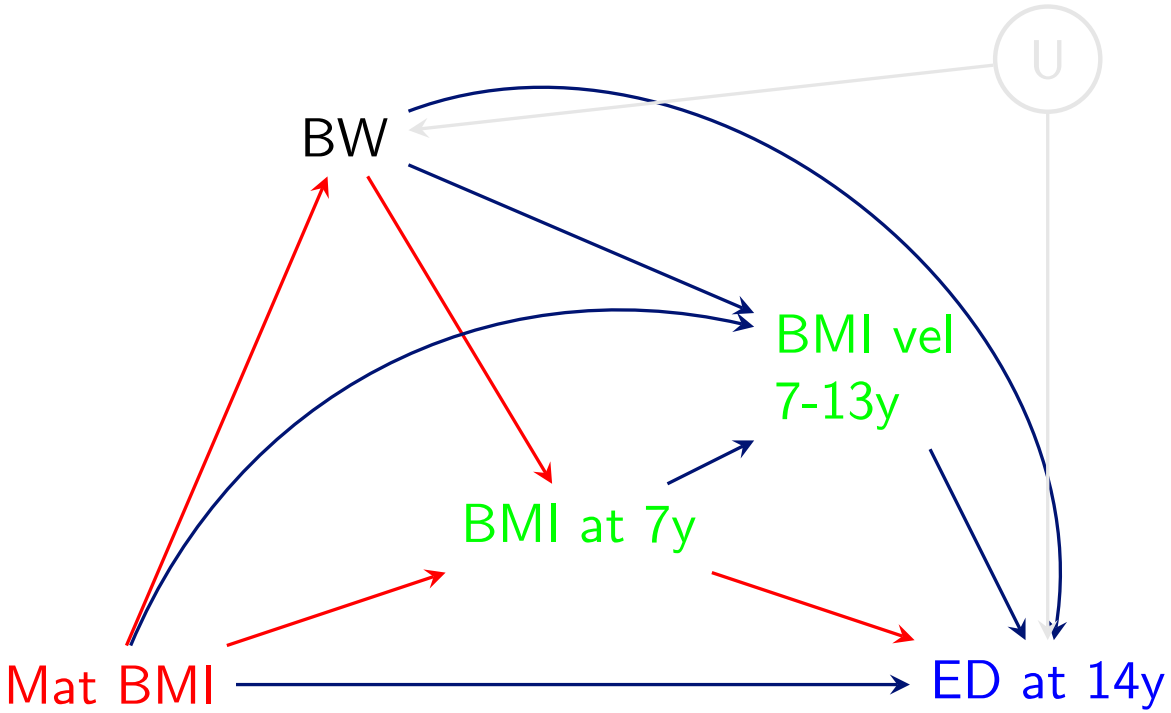


- There are now 4 possible decompositions.

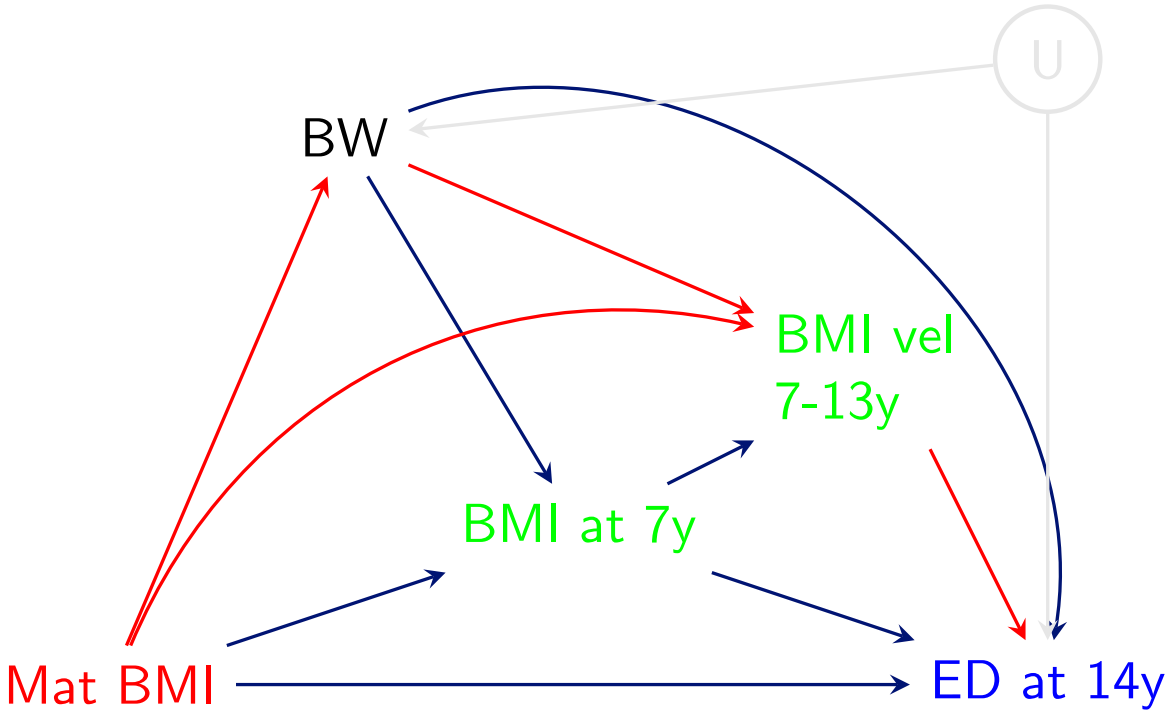
More complex mediated effects

1. Mediating paths via BMI at 7y alone



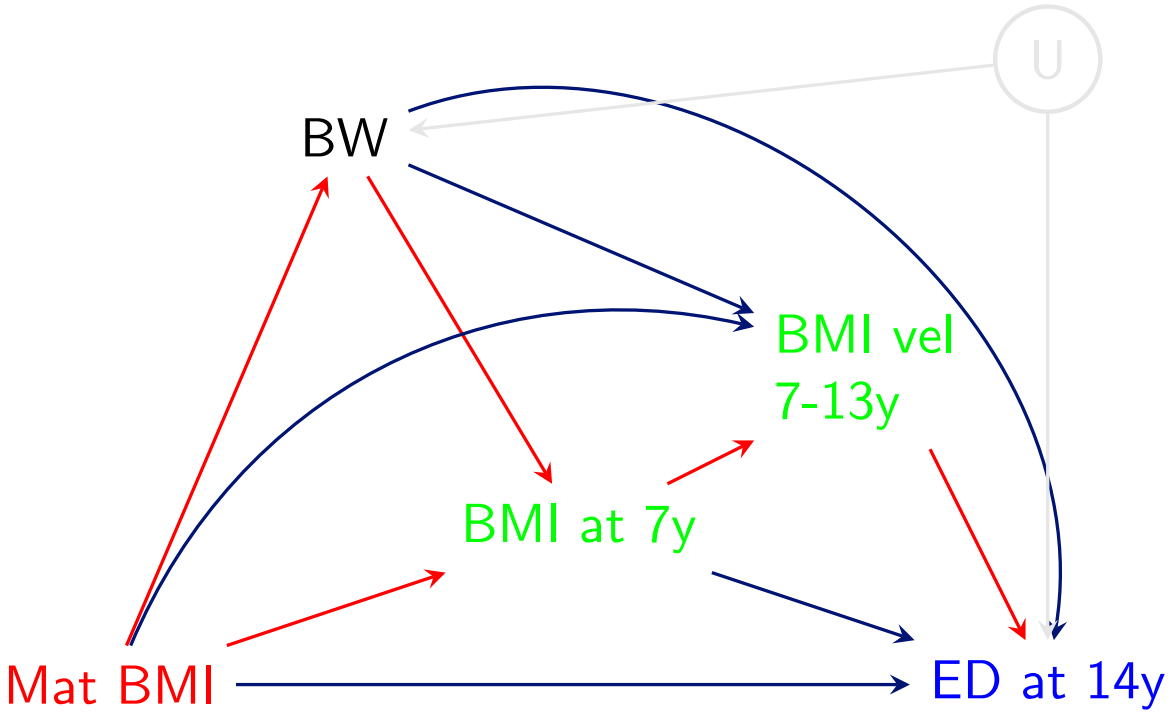
More complex mediated effects

2. Mediating paths via BMI velocity alone



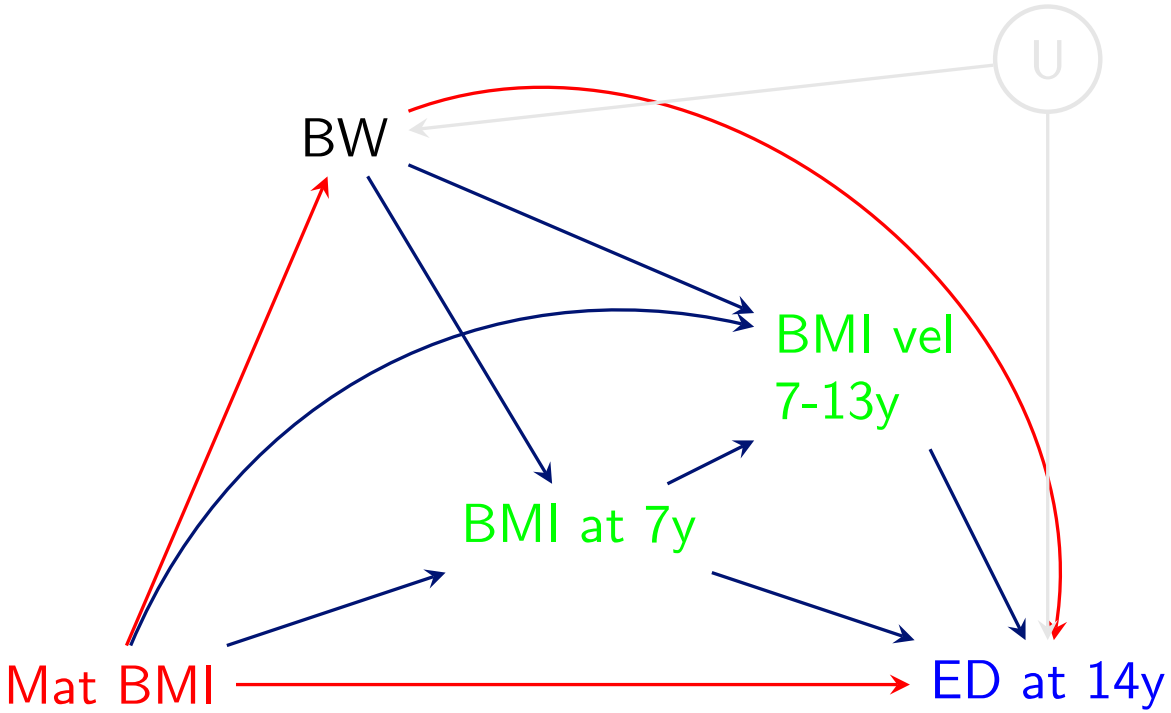
More complex mediated effects

3. Mediating paths via both BMI at 7 and BMI velocity



More complex mediated effects

4. Not mediated by either BMI at 7 or BMI velocity



Comments

- Queries such as these require careful thinking about what are the mediators of interest.
- Current methodology has not yet fully dealt with issues of multiple mediators: there are issues of numbers (*e.g.* with 3 mediators of interest, instead of 4, there are 8 mediating components) and also of identifying assumptions.
- If there are interactions/non-linearities, an additional complication arises from how to apportion the contribution of these to the various pathways.
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Outline

Hygienic thinking and exotic methods

- These three examples were meant to make the case for thinking hygienically before embarking on any analysis.
- In order to practise the best of statistics in medical research we need to:
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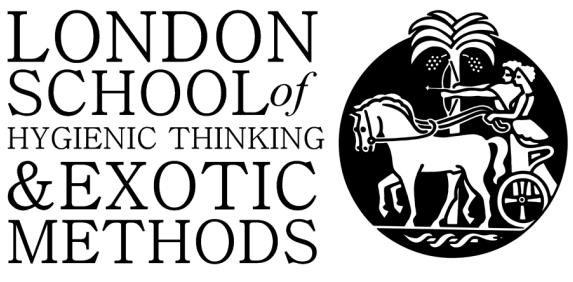
There is a role for all of us, as long as . . . we think hygienically!



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Grazie!

Grazie di tutto!

With a special thought for Giannina e Walter.

Outline

References

- De Stavola BL, dos Santos Silva I, McCormack V, Hardy RJ, Kuh DJ, Wadsworth MEJ (2004). Childhood growth and breast cancer. *American Journal of Epidemiology*, **159**(7):671–682.
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- Daniel RM, De Stavola BL, Cousens SN and Vansteelandt S (*under revision*). Causal mediation analysis with multiple mediators.