PATHWAYS

PATHWAYS
biosocial influences on health

Social disadvantage and infant mortality

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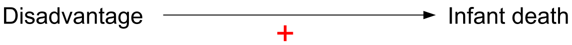
Infant mortality

- Infant mortality is strongly patterned by socio-economic conditions, even in developed countries (Melve *et al.* 2003).
- It is also strongly and negatively related to birth weight (BW), with the gradient seen even in babies born at term (Wilcox, 2001).
- BW is related to socioeconomic circumstances, with poverty consistently associated with low birth weight (Paneth, 1995)
- This suggests that BW may explain at least some of the positive association between disadvantage and infant mortality, *i.e.* it may act as one of the mediators.



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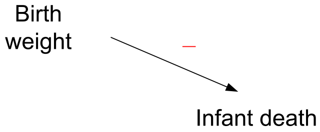

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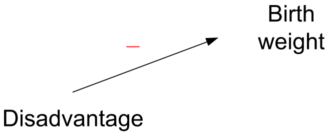

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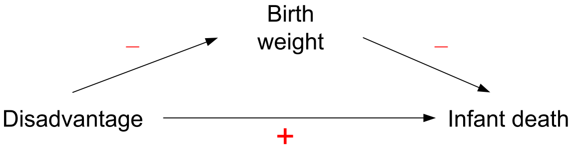
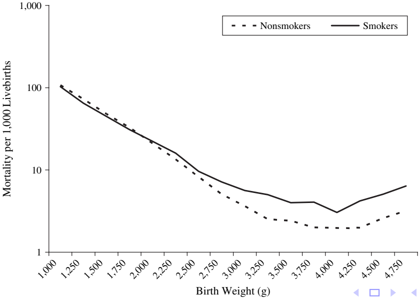


The low birth weight paradox

There is also evidence that shows that the risks associated with low BW vary between population subgroups, *e.g.* :

- babies born to mothers who smoked during pregnancy are usually 100-200g lighter at birth than babies of non-smoking mothers,
- yet, for a given low BW, those exposed to maternal smoking are at lower risk of infant mortality than those unexposed.



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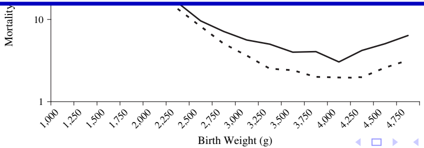
- This apparent effect modification is seen for other disadvantaged groups.
- However, recent contributions have argued that this is an artifact of the analytical approach used (*e.g.* Hernández-Díaz, 2006).



Aims of the talk

- Interest in the UK setting
- Specifically: *whether the effect of Disadvantage on infant mortality*:

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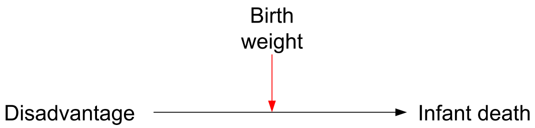

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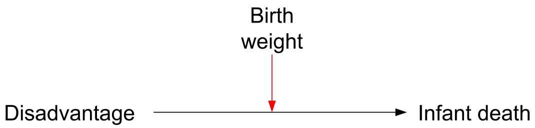

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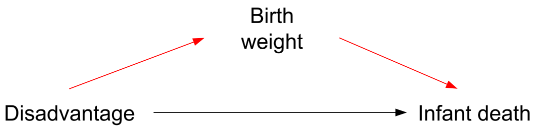

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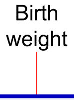

Using ONS Longitudinal Study (births in 1981-2009)

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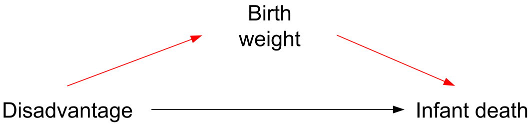


Outline

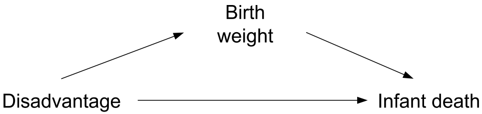
A quick revision of this morning lecture

Causal effects and diagrams

- The questions posed above imply that we are interested in causal effects, *i.e.* what would happen to the outcome if we change the value of the exposure from 0 to 1.
- This calls upon quantities that are not all observable—*i.e. potential outcomes*—and leads to formal definitions of total, direct, and indirect effects.
- To estimate these quantities from the observed data we need to state explicitly our assumptions, most naturally via a diagram where all important factors are included, even if unmeasured.

Alternative diagrams

To answer either question we need to state explicitly our assumptions.
Say we assume our world to be:
A:



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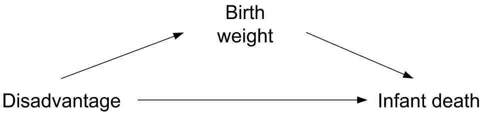
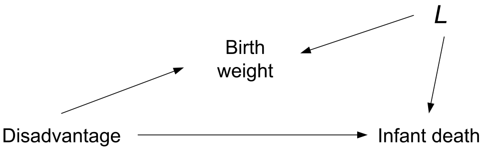


B:



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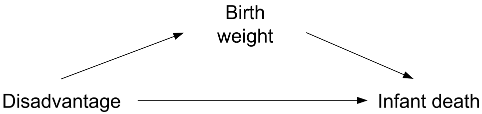
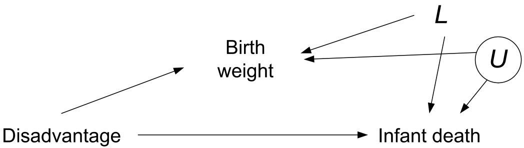


C:



The analytical challenges for question 1 (effect modification)

Scenario A

Say the world is as in A:

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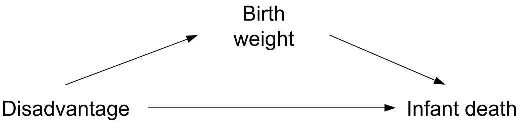

What happens if we stratify the analyses by BW?

The analytical challenges for question 1 (effect modification)

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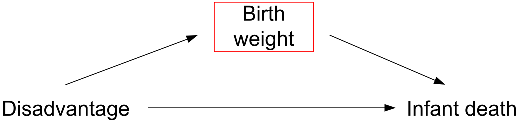

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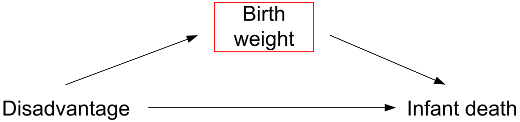

What happens if we stratify the analyses by BW?

- If the diagram is correct, we would obtain unbiased estimate of BW-specific effects of *Disadvantage*.
- This can be achieved by standard regression methods, with an interaction term added to the model for *Infant death*.

The analytical challenges for question 1 (effect modification)

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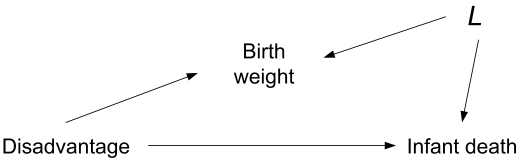

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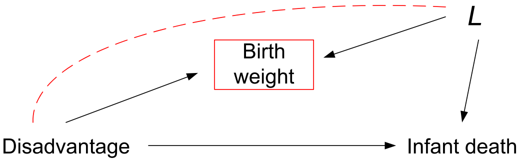

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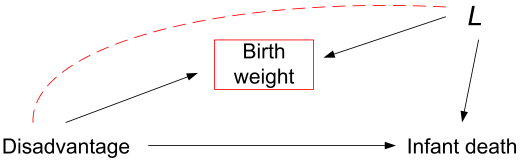

What happens if we stratify by BW?

- The association between the variables that directly influence BW is altered,
- the effect in each stratum of BW becomes biased.

The analytical challenges for question 1 (effect modification)

Scenario B

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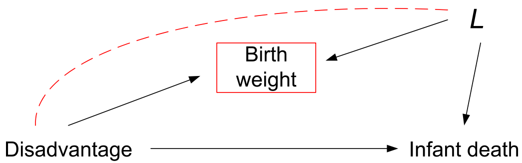

What happens if we stratify by BW?

- The association between the variables that directly influence BW is altered,

Solution:

- We should also control for L (*e.g.* in the regression model).

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Scenario C

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The analytical challenges for question 1 (effect modification)

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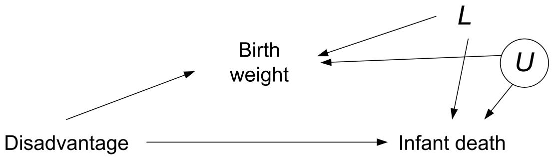

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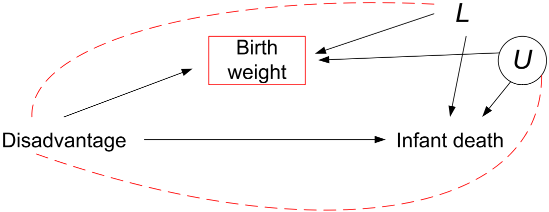

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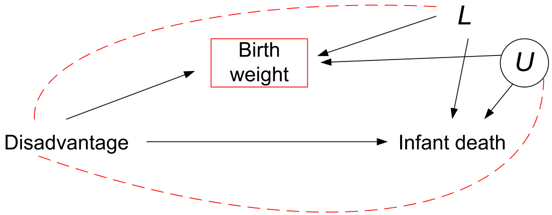

What happens if we stratify by BW?

- controlling for U is not an option because it is not observed.

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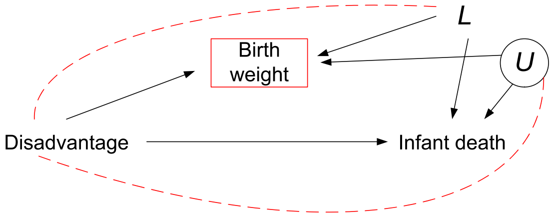


What happens if we stratify by BW?

Solution:

- conditioning on predicted risk of low BW
  (instead of observed BW; VanderWeele, 2012)
- sensitivity analyses

The analytical challenges for question 2 (Mediation)

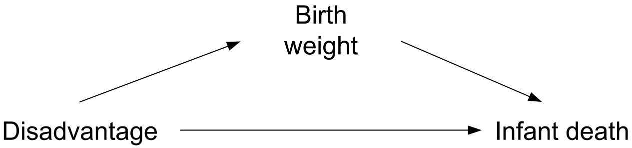
Revision of this morning lecture

- If we aim to partition the causal effect of *Disadvantage* into *direct* and *indirect* effects we have several options.
- Standard regression methods can be used only in simple settings,

The analytical challenges for question 2 (Mediation)

Revision of this morning lecture

- If we aim to partition the causal effect of *Disadvantage* into *direct* and *indirect* effects we have several options.
- Standard regression methods can be used only in simple settings, such as A[1]



[1] with continuous outcomes

The analytical challenges for question 2 (Mediation)

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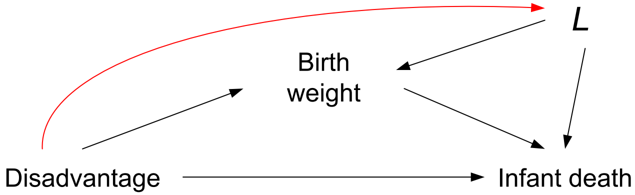
- If we aim to partition the causal effect of *Disadvantage* into *direct* and *indirect* effects we have several options.
- Standard regression methods can be used only in simple settings, but not in D (*intermediate confounding*):



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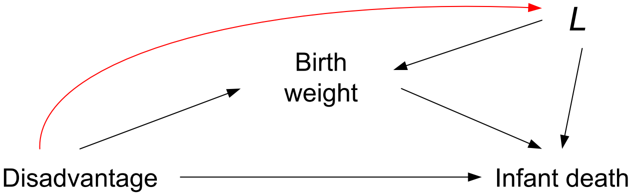

- In such settings alternative methods, *e.g.* G-computation, can be used (Vansteelandt, 2012).

The ONS Longitudinal Study

The Office for National Statistics Longitudinal Study (ONS LS):

- Record linkage study set up in 1974 (see http://celsius.lshtm.ac.uk/)
- Comprises linked census and event (and thus infant mortality[1]) records for 1% of the population of England and Wales (about 500,000 people at any one census)
- Includes BW of babies born to LS mothers (regularly since 1981, recorded at registration)
- Several indicator of social disadvantage: here we show results for maternal education

[1] death within 1st year of life

The study population

- 191,589 singleton live births in 1981-2009 (98,124 males, 93,465 females)
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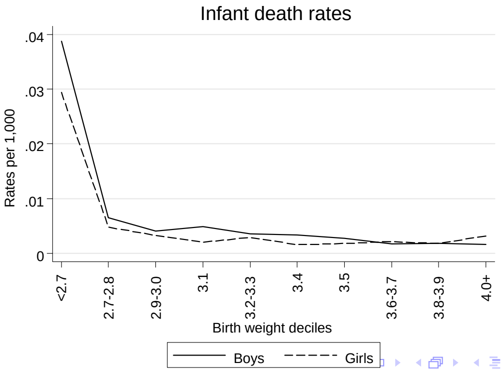

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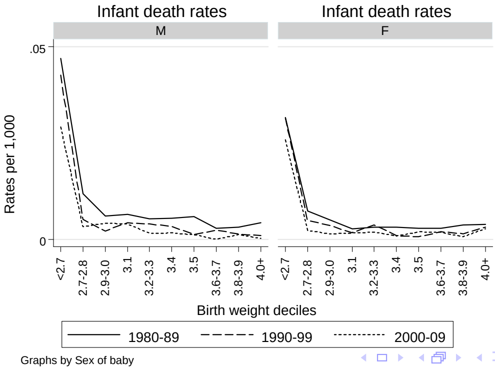
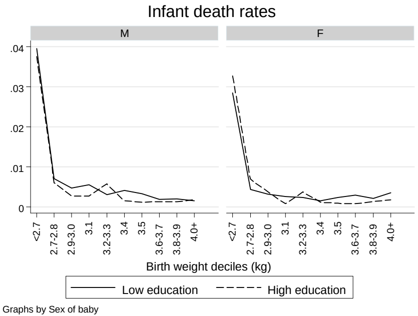
- Among them, 1,139 infant deaths (620 males, 519 females)
- Mortality rates vary greatly by BW and moderately by sex, and have also improved with calendar time:



Question 1

Is the effect of maternal education modified by birth weight?



- Similar picture to that seen with US data:

  apparent absence (or even reversal) of effect when BW<2.5 kg:
  low birth babies may not be as affected by Disadvantage

Note: Maternal education information for 94%: greater missingness in non-white mothers and recent births

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Is the effect of maternal education modified by birth weight?

Restricting the analyses to white mothers:

	Birth weight ≥ 2.5 kg		Birth weight < 2.5 kg	
Mat Education	*Low*	*High*	*Low*	*High*
Births	108,023	42,411	6,852	1,801
Deaths	355	110	336	98
Rates (× 1,000)	3.29	2.59	49.04	54.41
Crude OR	**1.27** (1.02, 1.57)		**0.90** (0.72, 1.12)	
heterog test (p)		*(0.031)*		
Adjusted[2] OR	**1.24** (1.00, 1.54)		**0.88** (0.70, 1.11)	
heterog test (p)		*(0.036)*		

[2] Adjusted for sex, year birth, region, and accounting for clustering

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Evidence of effect modification by low BW

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These results are stratified by BW and account for confounding by sex, year birth and region[3].

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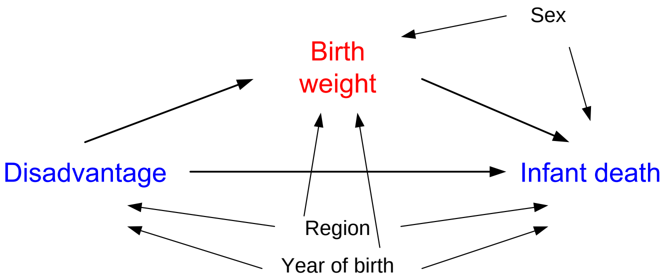

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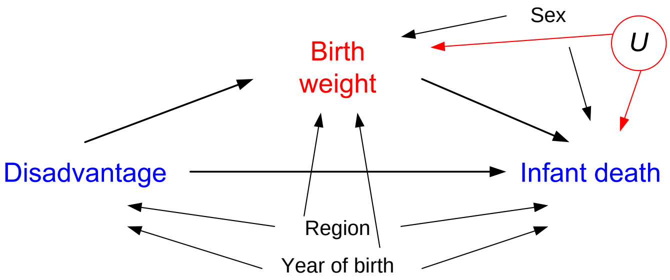

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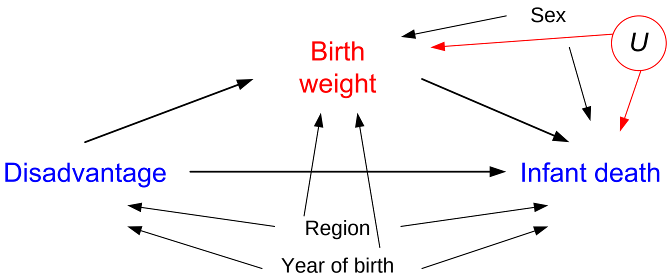

If so, the results would be biased.

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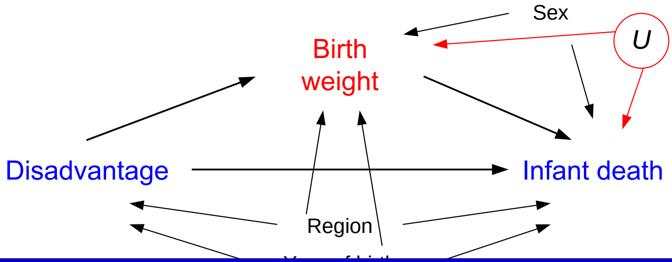

Alternative method:

Stratifying the analyses by predicted risk of low BW

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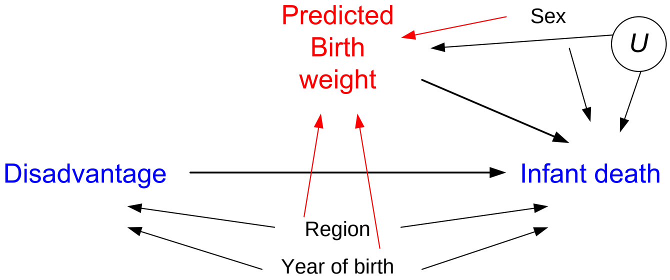

An alternative approach

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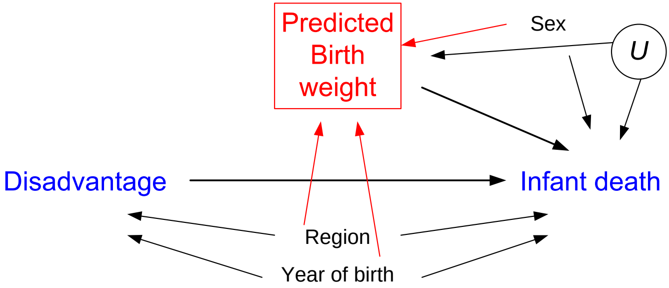
This method consist of:

- predicting low BW risk using confounders only
- conditioning on it to find stratum-specific effects (low & high risk) does NOT introduce spurious associations



Stratifying by predicted risk of low BW: results

Effect of low maternal education, white mothers only:

Definition of high risk	Low risk OR	Low risk (95% CI)	High risk OR	High risk (95% CI)	*p-value* (heterog.)
Observed[4]	1.24	(1.00, 1.54)	0.88	(0.70, 1.11)	0.04
>95th centile[5]	1.26	(1.07, 1.49)	1.14	(0.57, 2.27)	0.77

[4] Adjusted for sex, year birth, region, and accounting for clustering
[5] Accounting for clustering

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>95th centile[5]	1.26	(1.07, 1.49)	1.14	(0.57, 2.27)	0.77

No evidence of effect modification by low BW,
but possibly of unmeasured confounding.

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Question 2

Does BW mediate the effect of low maternal education on infant mortality?

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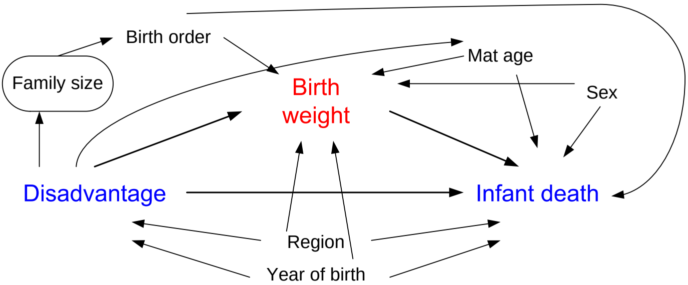

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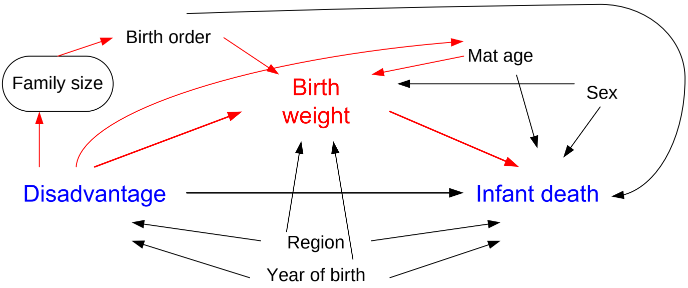

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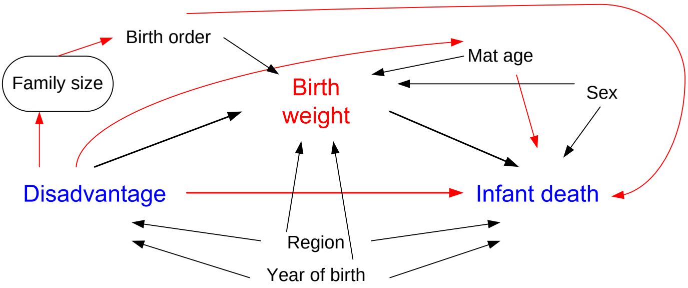

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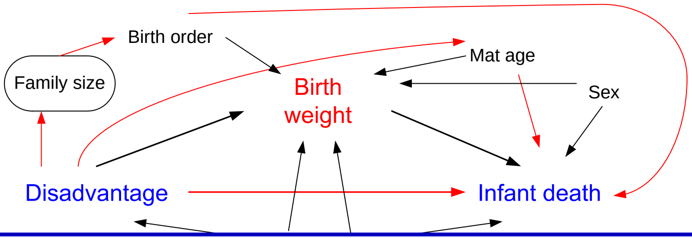

There are intermediate confounders: hence use G-computation (Daniel, et al, 2011).

Question 2

Causal parameters of interest (ignoring the confounders in these definitions; Vansteelandt, 2012)

- The total causal effect (TCE):

$$TCE^{OR} = \frac{E[Y(1)]/\{1 - E[Y(1)]\}}{E[Y(0)]/\{1 - E[Y(0)]\}}$$

- The natural direct effect (NDE):

$$NDE^{OR} = \frac{E[Y(1, M(0))]/\{1 - E[Y(1, M(0))]\}}{E[Y(0, M(0))]/\{1 - E[Y(0, M(0))]\}}$$

- The natural indirect effect (NIE):

$$NIE^{OR} = \frac{E[Y(1, M(1))]/\{1 - E[Y(1, M(1))]\}}{E[Y(1, M(0))]/\{[1 - E[Y(1, M(0))]]\}}$$

where $Y(x)$ is the potential value of Y that would have occurred had X been set to x and $Y(x, m)$ the potential value of Y that would have occurred had X been set to x and M to m

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- The natural indirect effect (NIE):

- G-computation allows us to estimate these effects
- Here assuming: consistency, conditional exchangeability, and no individual X-M interaction

G-computation of natural direct and indirect effects

Effect of low maternal education mediated and not mediated by low BW[6]: white mothers only

	OR	(95% CI)
Natural direct effect	1.18	(0.82, 1.69)
Natural indirect effect	1.22	(0.98, 1.52)
Total causal effect	1.44	(1.05, 1.97)

- There is a harmful total effect of low maternal education
- This effect appears to be partly mediated by low BW
- Results depend on assumption of no unmeasured confounding: need for sensitivity analyses (Imai et al, 2010).

[6] Fitted on one randomly selected child per mother, restricted to white mothers

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Specific comments

- Effect modification by birth weight not supported by analyses that allow for unmeasured confounding
- Effect of maternal education appears to be mediated by birth weight, but only partly
- Results are based on a representative sample of the general population, however bias due to unmeasured confounding cannot be discounted

General comments

- Issues arising in perinatal epidemiology when studying effect modification and mediation are extremely complex.
- Standard regression methods are generally inadequate, unless the setting is very simple.
- Need for stating explicitly all putative causal relations, not only among the variables of interest, but also those involving variables that may influence them.
- Overall, there should be more awareness of:
  - potential biases arising from unmeasured confounding
  - alternative estimating methods

Acknowledgements and thanks

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The permission of the Office for National Statistics to use the Longitudinal Study is gratefully acknowledged, as is the help provided by staff of CeLSIUS.
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