PATHWAYS

PATHWAYS biosocial influences on health

Social disadvantage and infant mortality:

the birth weight paradox revisited

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Infant mortality and disadvantage

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First observed by Yerushalmy (1964, 1971) and interpreted as BW modifying the effect of many factors associated with infant mortality:

BW paradox

Example

- Smoking known risk factor for low BW.
- Low BW babies born to smokers lower mortality than those of non-smokers:

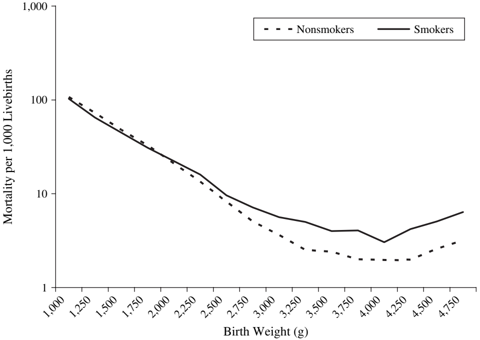
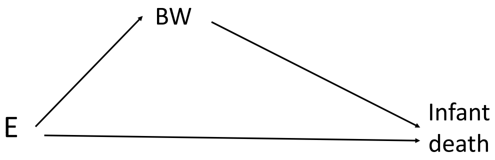


Figure: Birth-weight-specific infant mortality curves, US, 1991 (Hernandez-Diaz, AJE 2006)

Outline

The low birth weight paradox: collider bias?

- BW is on the causal pathway from “Disadvantage” (E) to ”Infant death”, but there are unmeasured confounders U_1.
- Comparing infant mortality rates at given values of BW leads to opening up a spurious path from E to “Infant death” (Hernandez-Diaz *et al.* , 2006).
- Paradox explained with U_1 and U_2 acting in opposite directions (Basso *et al.* , 2006 & 2009)



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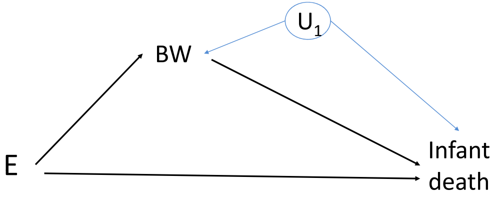

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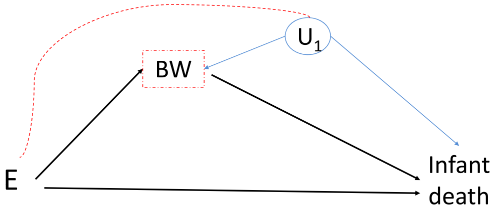

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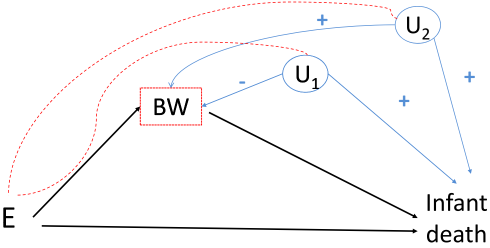
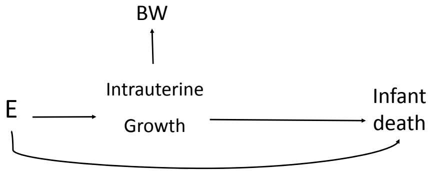


Low BW is a crude measure of the mechanism of the exposure E, "Disadvantage":

- It is only a proxy of intrauterine growth rate and time,
- neither intrauterine dimensions are usually available in large observational studies.
- Other pathways may link exposure to the infant mortality (hence the added arrows).



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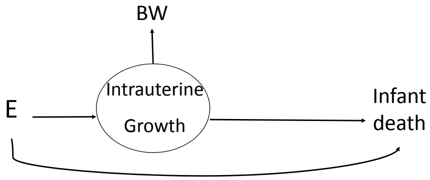

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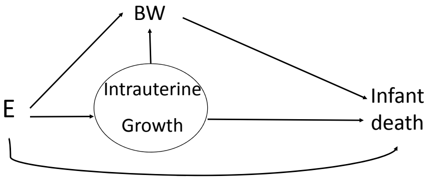

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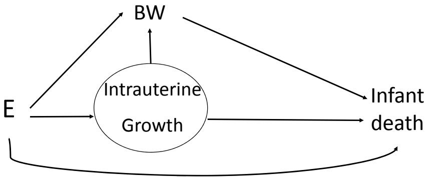
But how can we proceed without information on intrauterine growth?

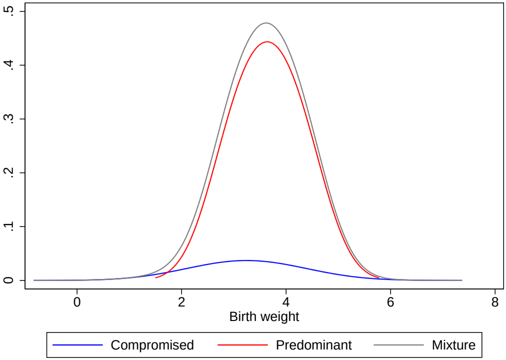


Wilcox Birth weight model

Wilcox (1983,2001) suggested that there are two sub-populations of newborns:

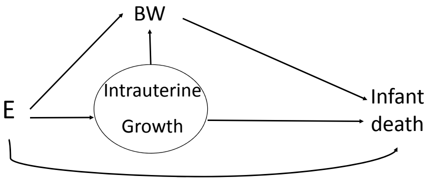
(a) predominant: mostly term babies,

(b) compromised: mostly pre-term babies and small-for-gestational-age.



Reformulated alternative model

- The model can be reformulated in terms of these classes.
- Assuming that the birth weight distribution for each sub-population is normal,
- and including predictors, we can estimate Prob(class = compromised) using Latent Class Modeling.



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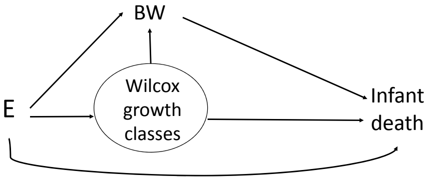

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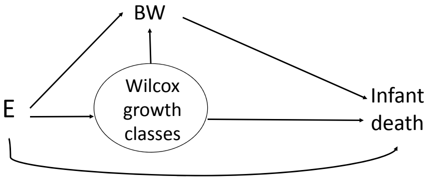

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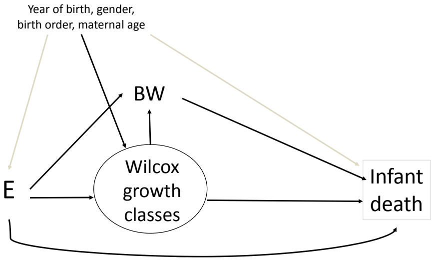

With this more general theoretical framework, we reconsider the two main questions.
Is BW:

1. an effect modifier of the effect of “Disadvantage” on Infant mortality?
2. a mediator for the effect of “Disadvantage” on Infant mortality?

Questions

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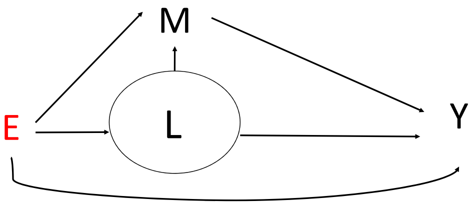
The extended mediation model

- BW: potential mediator (M); "Disadvantage": exposure (E); Infant mortality: outcome (Y); "Intrauterine growth": intermediate confounder (L).
- Replacing L with $\hat{L} = \Pr(L = 1)$ (1: compromised, 0: predominant),



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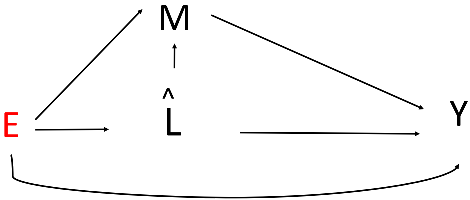

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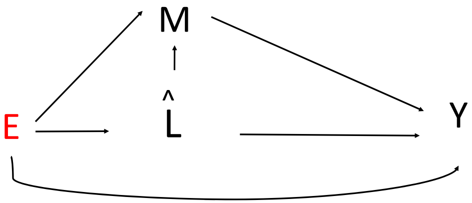
- If these effects are similar there is no support for effect modification by M.



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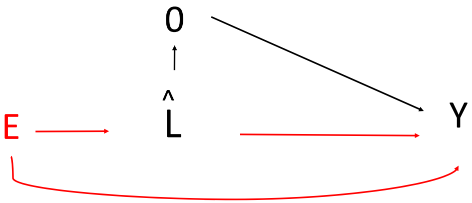

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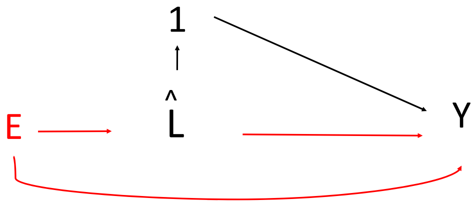

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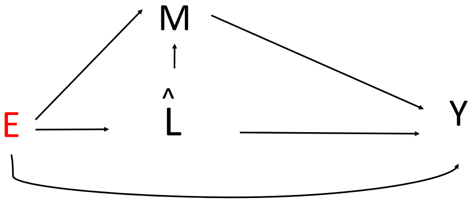

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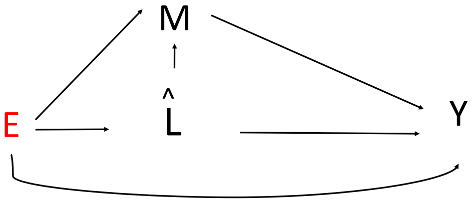

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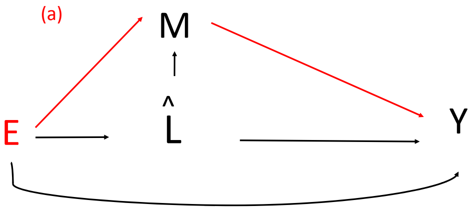

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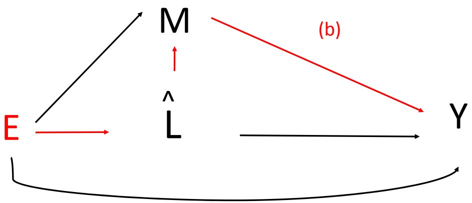

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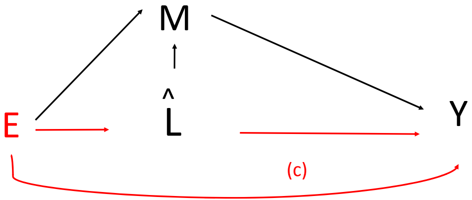

Estimands and their estimation

Estimands (CDE(m) and PNDE, TNIE) are expressed as OR contrasts.

Assumptions:

No interference, consistency, conditional exchangeability, and, because of L, either:

- No E–M interaction:Model I (Robins and Greenland, 1992).
- No non-linearities in L:Model II (Petersen *et al.* , 2006).

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- Record linkage study set up in 1974 (see http://celsius.lshtm.ac.uk/).
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- Includes BW of babies born to LS mothers (regularly since 1981, recorded at registration).
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The study population

- 160,366 singleton live births in 1981-2011.
- *E*: 38% of mother with fewer that 5 O-levels ("Low education").
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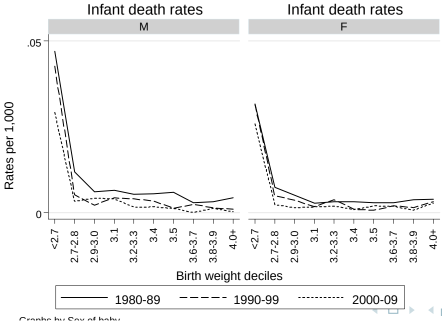

Natural direct and indirect effects of low maternal education

VERY PRELIMINARY RESULTS- SEs not yet corrected

	Model I		Model II	
	ln OR	**(SE)**	ln OR	**(SE)**
CDE(0)	–	–	0.205	(0.076)
CDE(1)	–	–	0.206	(0.076)
PNDE	0.221	(0.082)	0.227	(0.077)
TNIE	0.011	(0.007)	-0.012	(0.005)
TCE	0.232	(0.082)	0.205	(0.076)

- Model I and II give similar results, despite the difference in assumptions.
- CDE(0) and CDE(1) from Model II are very similar: no evidence of effect modification.
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Critique

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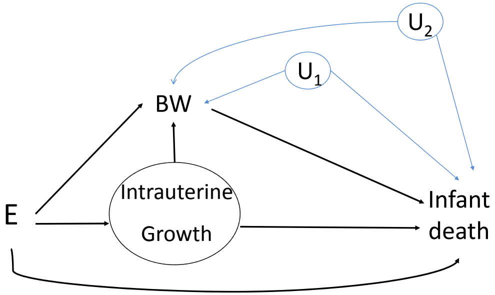
- However, not if U_1 and U_2 influenced L directly.



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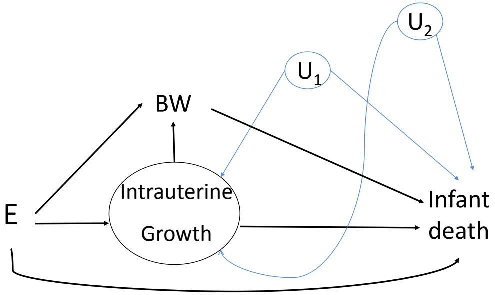

Conclusions

- Approach may contribute to the debate about the BW paradox by representing the underlying biological process via a latent variable.
- Results depends on strong and partly unverifiable assumptions, although similarity of results from alternative parametric specifications are reassuring.
- Estimation of mediation effects and their SEs raises several problems. There are issues with:
  - estimation of the class probability,
  - correlations among the outcomes of siblings,
  - instability due to small number of events.
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Acknowledgements

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The authors alone are responsible for the interpretation of the data.

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Additional slides

Estimands 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

Maternal education and infant mortality

Mat Education	**Birth weight $\geq$ 2.5 kg** *Low*	*High*	**Birth weight $<$ 2.5 kg** *Low*	*High*
Births	92,704	59,141	4,393	4,128
Deaths	220	222	225	195
Rates (x 1,000)	2.4	3.8	51.24	47.2
Sex-adjusted OR	**1.58** (1.31, 1.91)		**0.92** (0.76, 1.12)	
heterog test (p)		*(0.031)*		
Adjusted[2] OR	**1.23** (1.01, 1.49)		**0.92** (0.76, 1.12)	
heterog test (p)		*(0.036)*		

The Wilcox model

	Variable	Class 1	Class 2
For μ			
	Intercept	3.51	3.65
	sex	-	-
	year birth	-	+
	mat age	+	+
	birth order	-	+
For σ			
	Intercept	0.90	0.45
For π			
	sex	-	
	Mat educ	+	

About 10% of births predicted to be “compromised”.

Further Critique

- There is another source of bias: conditioning on live birth.
- Still births are a form of competing event, reducing the denominator of possible infant deaths.
- Consider the composite outcome of Infant death or Still birth (Kramer *et al.* , 2014):

	Only Infant deaths Model I		Only Infant deaths & Still births Model II	
	ln OR	**(SE)**	ln OR	**(SE)**
PNDE	0.221	(0.082)	0.174	(0.067)
TNIE	0.011	(0.007)	0.018	(0.008)
TCE	0.232	(0.082)	0.192	(0.066)