PATHWAYS

Social disadvantage and infant mortality:

the birth weight paradox revisited

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UK Census-based Longitudinal Studies Meeting · 31 March 2015

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Socio-economic disadvantage and 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).
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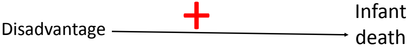

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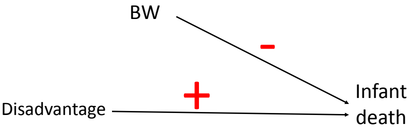

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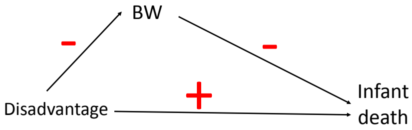

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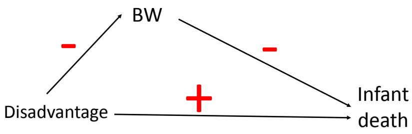

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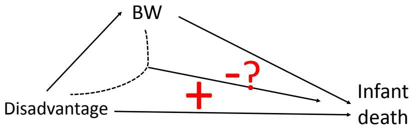

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Aim of the talk

Study the mediating role of BW using 30 years data from ONS LS.

Outline

1. Background
2. Methods
3. Results
4. Conclusions

Outline

Low birth weight paradox

- First observed with regards to smoking: low BW babies born to smokers have lower mortality than those of non-smokers.

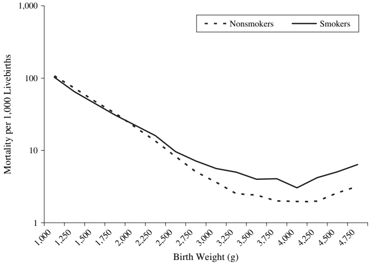

Figure: Birth-weight-specific infant mortality curves, US, 1991

- Also found for other high-risk populations (*e.g.* defined by social class, ethnicity, region) (Yerushalmy (1964, 1971), Hernandez-Diaz (2006)).

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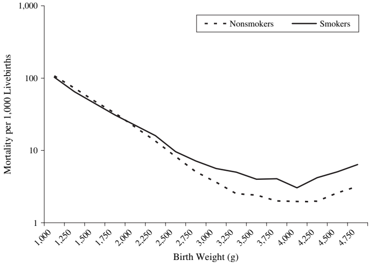

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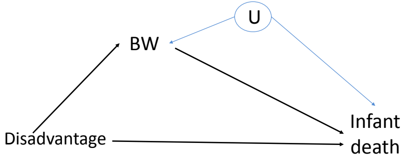
An explanation of the low BW paradox

- There are unmeasured confounders U between BW and Infant death.
- Comparing rates by disadvantage at given values of BW . . .

  opens up a spurious path from disadvantage to death.

  "Low BW may occur because of disadvantage or U (or both): knowing the disadvantage status of a baby is informative of his/her U, hence the induced association."
- Reasonable values of U → BW and U → death sufficient to explain this paradox.



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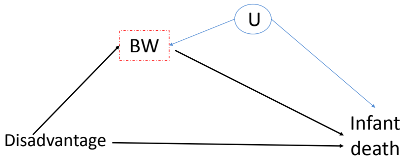

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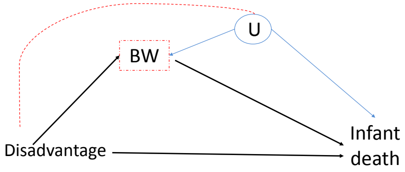

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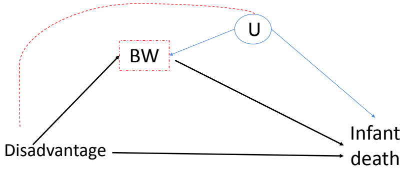

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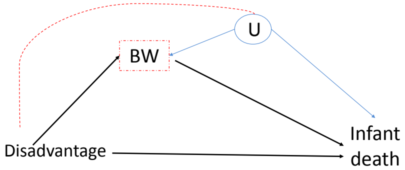

Implication for studying BW as a mediator

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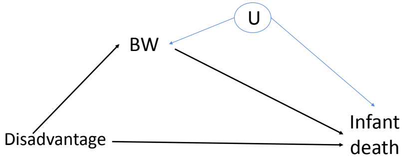

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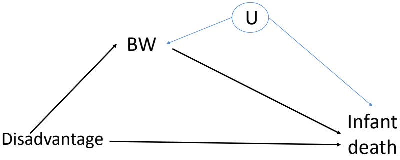

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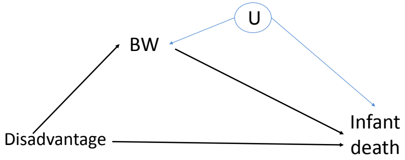

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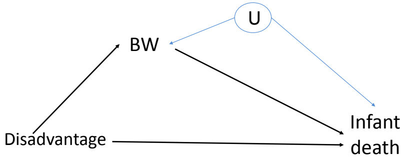

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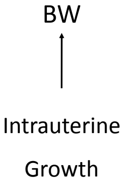
Outline

An informed approach to unmeasured confounding

- BW is a crude measure: it is only a proxy for intrauterine growth.
- Intrauterine growth likely to lie on pathways from Disadvantage to Infant death . . .
- and hence to confound the BW to Infant death relationship.
- Data on intrauterine growth not generally available.
- If diagram is correct, intrauterine growth plays role of *U*.



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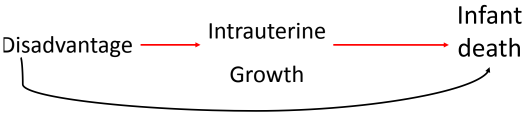

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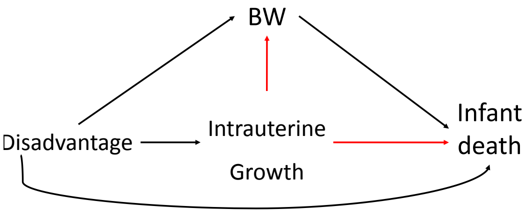

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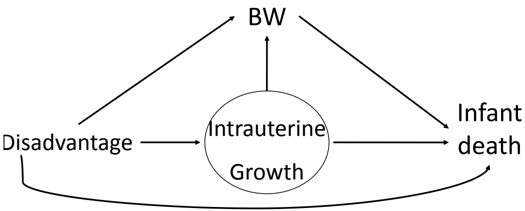

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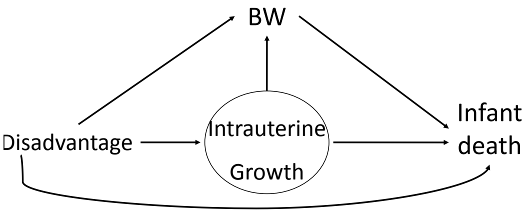

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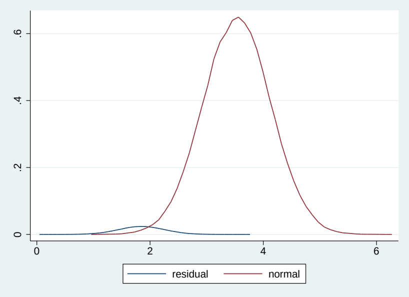

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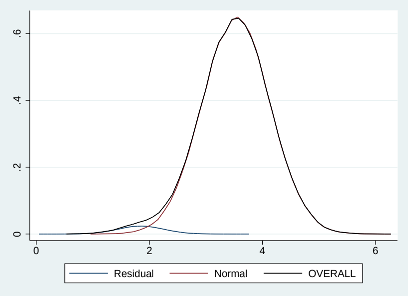

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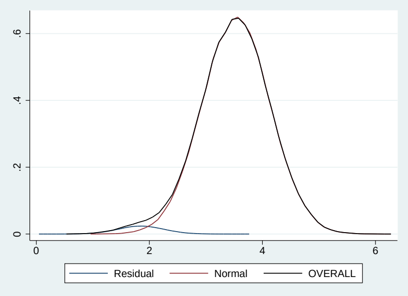
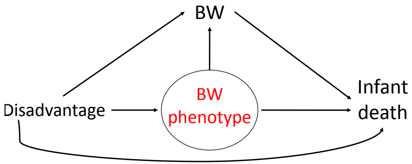


Reformulated Wilcox model

- Assume:
  - there are a number of latent BW phenotypes (classes)
  - BW for each class is normal
  - there are measured predictors for these distributions (in blue) and for the Prob(Class) (in red)
- Then we can use Latent Class Modelling to impute the missing value of BW phenotype.



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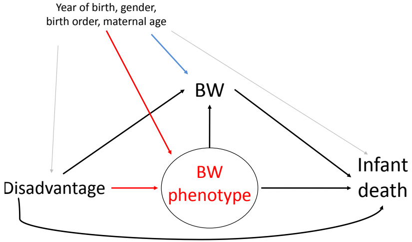

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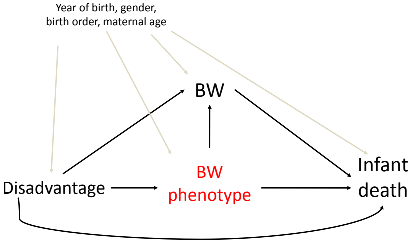

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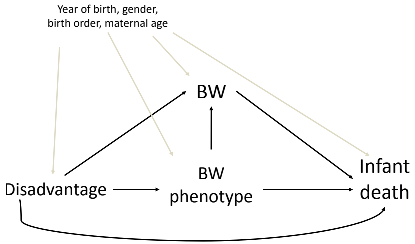

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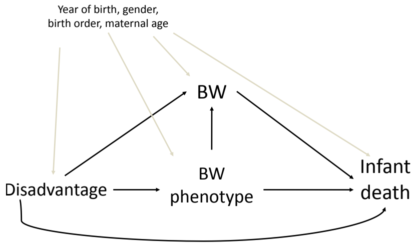

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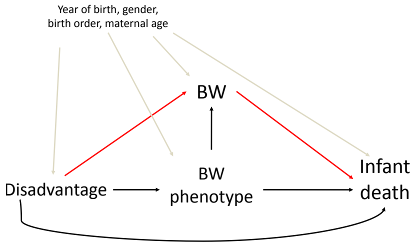

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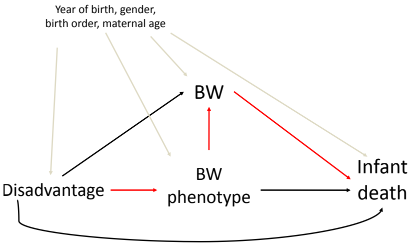

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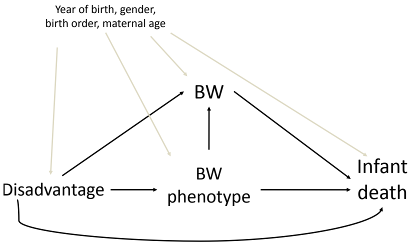

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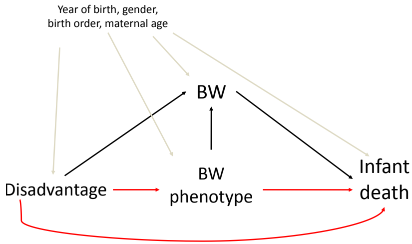

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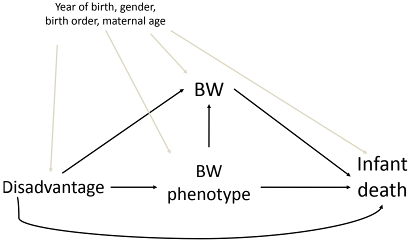

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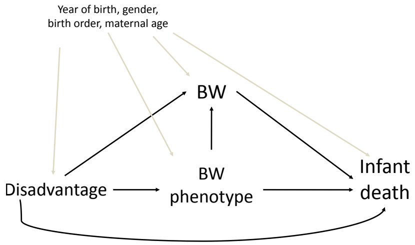

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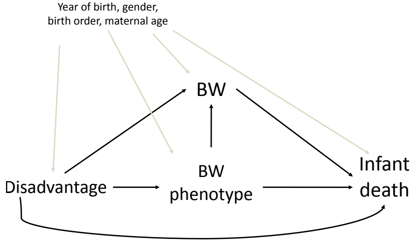

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We estimate them as Natural Direct (NDE) and Natural Indirect Effects (NIE)[a] (on the OR scale), using Monte Carlo G-computation with bootstrapped SEs (to account for the imputation step; Daniel *et al.* , 2011).

[a] More precisely,randomized interventional analogies of NDE and NIE (VanderWeele *et al.* (2014)).

Outline

The England and Wales ONS Longitudinal Study

- Record linkage study set up in 1974 (see http://www.ucl.ac.uk/celsius/).
- Comprises linked census and event (and thus infant mortality 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 (recorded at registration).
- Several indicator of social disadvantage
- Restrictions:
  - singleton births to white mothers (∼85%)
  - births from 1981 to ensure coverage

The study population

- 168,472 singleton live births in 1981-2012.
- *E*:
  - 38% of mothers with fewer that 5 O-levels
  - 41% of parents in manual occupation
- *M*: 5.4% with birth weight$<$2.5kg.
- *Y*: 0.58% (973) infant deaths.

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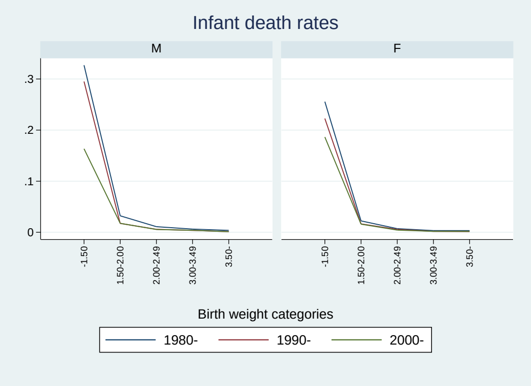
Infant mortality rates

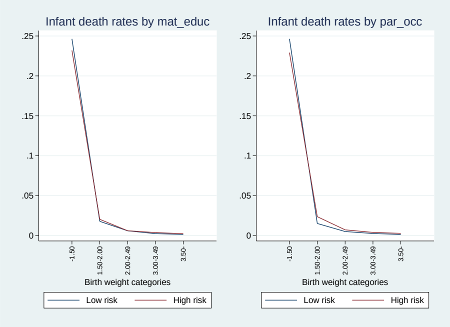
Mortality rates vary greatly by BW, moderately by sex, improving with calendar time:



Source: E&W ONS LS

Rates by socio-economic disadvantage and BW

Apparent reversal of effect at the lower end of BW:



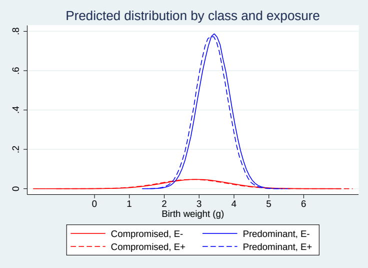
OR	0.90	1.08	0.97	1.48	1.51	0.65	1.12	1.34	1.08	1.38
p-value			0.03					0.01		

Source: E&W ONS LS

Predicted latent class distributions

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

About 11% of births predicted to be "compromised".



- Mean BW: 3.43 (SD=0.45) and 2.92 (SD=0.92)
- OR of being in compromised class is 1.36 (1.25, 1.47) when exposed to low maternal education.
- Shifted by -0.10 (-0.15, -0.06) and -0.08 (-0.08, -0.07) when exposed.

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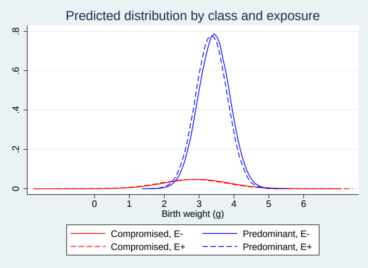

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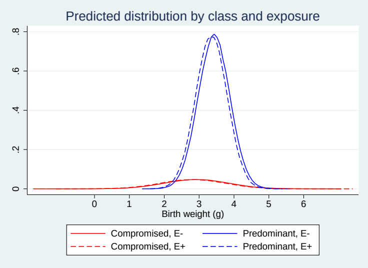

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Similar results when exposed to parental manual occupation.

Source: E&W ONS LS

Mediated effects

	Mat education			Par occupation		
	ln OR	(95% CI)	%	ln OR	(95% CI)	%
Controlling for latent class:						
TCE	1.43	(1.30, 1.63)	100.0	1.55	(1.48,1.77)	100.0
NDE	1.06	(0.93, 1.21)	15.5	1.13	(1.06, 1.30)	18.2
NIE	1.35	(1.08, 1.52)	84.5	1.38	(1.31, 1.46)	71.8
Not controlling for latent class:						
NDE	1.21	(1.05, 1.34)	55.4	1.35	(1.25, 1.49)	67.8
NIE	1.15	(1.14, 1.17)	43.6	1.15	(1.15, 1.16)	32.2

Source: E&W ONS LS

Outline

Conclusions

- Attempted to identify some of the unmeasured confounders that may explain the birth weight paradox.
- Results depends on strong and partly unverifiable assumptions for:
  - the representation of the underlying biological process via a latent variable
  - for the partitioning of direct and indirect effects.
- However, if correct, they should not suffer from confounding bias to the same extent as more traditional analyses.
- Data on other components of U (*e.g.* birth complications) would be required to fully control for confounding.

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Acknowledgements

This work is supported by the ESRC Pathways Node (Award ES/1025561/2) of the National Centre for Research Methodology.

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.

CeLSIUS is supported by the ESRC Census of Population Programme (Award Ref: ES/K000365/1).

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

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ADDITIONAL SLIDES

ORs by socio-economic disadvantage and BW

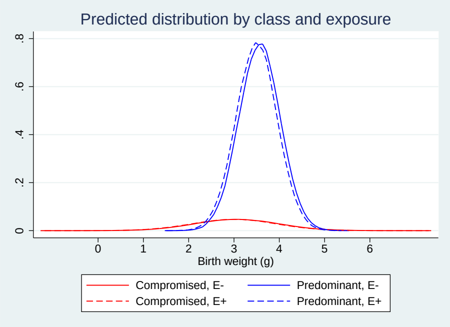
Effect modification by BW

BW (in kg)	M educ		P occup	
	OR	(95% CI)	OR	(95% CI)
Overall	1.32	(1.14, 1.51)	1.55	(1.36, 1.77)
p-value significance	<0.01		<0.001	
<1.5	0.90	(0.69, 1.18)	0.65	(0.43, 0.98)
1.5-2.00	1.08	(0.77, 1.52)	1.12	(0.71, 1.78)
2.0-2.49	0.97	(0.70, 1.33)	1.34	(0.98, 1.85)
3.0-3.49	1.48	(1.09, 1.99)	1.08	(0.71, 1.65)
≥ 3.5	1.51	(1.06, 2.15)	1.38	(0.86, 2.20)
p-value Interaction	0.03		0.01	

Average predicted latent class distributions

By parental occupation

About 11% of births predicted to be "compromised".



- similar BW, SD and shift.
- OR of being in compromised class is 1.40 (1.28, 1.53) when exposed.