Social disadvantage and infant mortality

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ESRC Research Methods Festival, 4th July 2012, 4pm
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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■ 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.
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.
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.

- 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 is modified by BW:

\[ \text{Disadvantage} \rightarrow \text{Birth weight} \rightarrow \text{Infant death} \]
Aims of the talk

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

(1) is *modified* by BW:

\[\text{Disadvantage} \rightarrow \text{Birth weight} \rightarrow \text{Infant death}\]

(2) is *mediated* by BW:

\[\text{Disadvantage} \rightarrow \text{Birth weight} \rightarrow \text{Infant death}\]
Aims of the talk

- Interest in the UK setting
- Specifically: *whether the effect of Disadvantage on infant mortality*:
  1. is modified by BW:
  2. is mediated by BW:

Using ONS Longitudinal Study (births in 1981-2009)

(1) is modified by BW:

(2) is mediated by BW:
1. Introduction

2. Analytical challenges
   - Question 1
   - Question 2

3. The ONS Longitudinal Study

4. Preliminary results
   - Question 1
   - Question 2

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

A:

- Birth weight
- Disadvantage
- Infant death
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A:

```
  Birth weight
 /               \
|                 |
|                 |
Disadvantage  →  Infant death
```

B:

```
  Birth weight
 /               \
|                 |
|                 |
Disadvantage  →  Infant death
```

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

A:

\begin{align*}
\text{Birth weight} & \quad \rightarrow \quad \text{Disadvantage} \quad \rightarrow \quad \text{Infant death} \\
\text{Birth weight} & \quad \rightarrow \quad \text{Infant death}
\end{align*}

C:

\begin{align*}
\text{Birth weight} & \quad \rightarrow \quad \text{Disadvantage} \quad \rightarrow \quad \text{Infant death} \\
\text{Birth weight} & \quad \rightarrow \quad \text{Infant death}
\end{align*}
The analytical challenges for question 1 (effect modification)

Scenario A

Say the world is as in A:
The analytical challenges for question 1 (effect modification)

Scenario A

Say the world is as in A:

- Birth weight
- Disadvantage
- Infant death

What happens if we stratify the analyses by BW?
The analytical challenges for question 1 (effect modification)

Scenario A

Say the world is as in A:

- Disadvantage → Birth weight → Infant death

What happens if we stratify the analyses by BW?
The analytical challenges for question 1 (effect modification)

Scenario A

Say the world is as in A:

![Diagram]

- 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*. 
Say the world is as in B:
The analytical challenges for question 1 (effect modification)

Scenario B

Say the world is as in B:

What happens if we stratify by BW?
The analytical challenges for question 1 (effect modification)

Scenario B

Say the world is as in B:

What happens if we stratify by BW?
Say the world is as in B:

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

Say the world is as in B:

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

**Solution:**

- We should also control for $L$ (e.g. in the regression model).
Say the world is as in C:
Say the world is as in C:

Disadvantage \( \rightarrow \) Birth weight \( \rightarrow \) Infant death

What happens if we stratify by BW?
Say the world is as in C:

What happens if we stratify by BW?
Say the world is as in C:

What happens if we stratify by BW?

- controlling for U is not an option because it is not observed.
Say the world is as in C:

What happens if we stratify by BW?

Solution:

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

- sensitivity analyses
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,
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
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*):

![Diagram](image-url)
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*):

  ![Diagram](image)

  - Disadvantage → Birth weight → Infant death

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

\(^1\)
\(^1\)death within 1st year of life
The study population

- **191,589** singleton live births in 1981-2009 (98,124 males, 93,465 females)
- Among them, **1,139** infant deaths (620 males, 519 females)
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The study population

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

![Graph showing infant death rates by sex and birth weight deciles](image)

- 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*
Question 1

*Is the effect of maternal education modified by birth weight?*

Restricting the analyses to white mothers:

<table>
<thead>
<tr>
<th>Mat Education</th>
<th>Birth weight $\geq 2.5$ kg</th>
<th>Birth weight $&lt; 2.5$ kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Births</td>
<td>108,023</td>
<td>42,411</td>
</tr>
<tr>
<td>Deaths</td>
<td>355</td>
<td>110</td>
</tr>
<tr>
<td>Rates (x 1,000)</td>
<td>3.29</td>
<td>2.59</td>
</tr>
<tr>
<td>Crude OR</td>
<td>1.27 (1.02, 1.57)</td>
<td>0.90 (0.72, 1.12)</td>
</tr>
<tr>
<td>heterog test (p)</td>
<td>(0.031)</td>
<td></td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>1.24 (1.00, 1.54)</td>
<td>0.88 (0.70, 1.11)</td>
</tr>
<tr>
<td>heterog test (p)</td>
<td>(0.036)</td>
<td></td>
</tr>
</tbody>
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$^2$ Adjusted for sex, year birth, region, and accounting for clustering.
### Question 1

**Is the effect of maternal education modified by birth weight?**

Restricting the analyses to white mothers:

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**Crude OR**

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- Birth weight < 2.5 kg: 0.90 (0.72, 1.12)

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**Adjusted OR**

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Evidence of effect modification by low BW

---

Adjustment for sex, year birth, region, and accounting for clustering.
These results are stratified by BW and account for confounding by sex, year birth and region. 

---

3 We do not control for maternal age or parity as these are on the causal path.
These results are stratified by BW and account for confounding by sex, year birth and region\textsuperscript{3}. These variables were selected on the basis of this conceptual diagram.

\textsuperscript{3}We do not control for maternal age or parity as these are on the causal path.
These results are stratified by BW and account for confounding by sex, year birth and region\(^3\).

These variables were selected on the basis of this conceptual diagram. However, it is likely that U is also present (e.g. congenital malformations):

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If so, the results would be biased.

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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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\[
\begin{align*}
\text{Disadvantage} & \quad \text{Birth weight} & \quad \text{Infant death} \\
\text{Region} & \quad \text{Year of birth} & \quad \text{Sex} & \quad \text{U}
\end{align*}
\]

Alternative method:
Stratifying the analyses by predicted risk of low BW

\(^3\)We do not control for maternal age or parity as these are on the causal path.
An alternative approach
Stratifying by predicted risk (VanderWeele, 2012)

This method consist of:

- predicting low BW risk using confounders only
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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
Effect of low maternal education, white mothers only:

<table>
<thead>
<tr>
<th>Definition of high risk</th>
<th>Low risk</th>
<th></th>
<th>High risk</th>
<th></th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>(95% CI)</td>
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<td>&gt;95th centile(^5)</td>
<td>1.26</td>
<td>(1.07, 1.49)</td>
<td>1.14</td>
<td>(0.57, 2.27)</td>
<td>0.77</td>
</tr>
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\(^4\) Adjusted for sex, year birth, region, and accounting for clustering
\(^5\) Accounting for clustering
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No evidence of effect modification by low BW, but possibly of unmeasured confounding.

---

^4 Adjusted for sex, year birth, region, and accounting for clustering

^5 Accounting for clustering
Question 2
Does BW mediate the effect of low maternal education on infant mortality?

To answer this question let's expand the diagram to include intermediate confounders.
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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
Effect of low maternal education mediated and not mediated by low BW\(^6\):

white mothers only

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<th>Effect</th>
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<tr>
<td>Total causal effect</td>
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- 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.
### Effect of low maternal education mediated and not mediated by low BW:

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6 Fitted on one randomly selected child per mother, restricted to white mothers.
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.
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:

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

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References


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