Social disadvantage and infant mortality: the birth weight paradox revisited

Bianca De Stavola
with Rhian Daniel, Richard Silverwood, Rachel Stuchbury, Emily Grundy

Research Methods Festival · 8 – 10 July 2014
Infant mortality (deaths <1 yr):
- negatively related to birth weight (BW)
- patterned by socio-economic conditions.
Infant mortality (deaths <1 yr):
- negatively related to birth weight (BW)
- patterned by socio-economic conditions.

Complication:
low BW babies in high-risk populations tend to have lower mortality rates than low BW babies in low-risk populations.
Infant mortality and disadvantage

Infant mortality (deaths <1 yr):
- negatively related to birth weight (BW)
- patterned by socio-economic conditions.

Complication:
low BW babies in high-risk populations tend to have lower mortality rates than low BW babies in low-risk populations.

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

BW paradox
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)
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).
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).
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).
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).
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).
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).
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).
An alternative explanation

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).

But how can we proceed without information on intrauterine growth?

Bianca De Stavola/BW Paradox
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.
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 \( \text{Prob}(\text{class} = \text{compromised}) \) using Latent Class Modelling.
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 \( \text{Prob}(\text{class} = \text{compromised}) \) using Latent Class Modelling.
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 $\text{Prob}(\text{class} = \text{compromised})$ using Latent Class Modelling.
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 \( \text{Prob}(\text{class} = \text{compromised}) \) using Latent Class Modelling.
Questions

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

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?
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),
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),
Question 1: is BW an effect modifier?

- We address the first question:
  - by comparing Controlled Direct Effect of $E$ on $Y$ holding $M$ at either 0 or 1.
  - If these effects are similar there is no support for effect modification by $M$. 

```
  E  \rightarrow M \leftarrow \hat{L} \rightarrow Y
```

Bianca De Stavola/BW Paradox
Question 1: is BW an effect modifier?

- We address the first question:
- by comparing Controlled Direct Effect of $E$ on $Y$ holding $M$ at either 0 or 1.
- If these effects are similar there is no support for effect modification by $M$. 
Question 1: is BW an effect modifier?

- We address the first question:
- by comparing Controlled Direct Effect of $E$ on $Y$ holding $M$ at either 0 or 1.
- If these effects are similar there is no support for effect modification by $M$. 

![Diagram of causal relationships]

E → L → Y

1

L

Hat
Question 2: is BW a mediator?

- We address the second question:
- by estimating the Natural Direct and Indirect Effects of $E$ on $Y$, where:
- the indirect effect is made of (a) and (b),
- and the direct effect is (c):
Question 2: is BW a mediator?

- We address the second question:
- by estimating the Natural Direct and Indirect Effects of $E$ on $Y$, where:
  - the indirect effect is made of (a)
  - and (b),
  - and the direct effect is (c):

![Diagram showing the relationship between E, M, L, Y]

Bianca De Stavola/BW Paradox 12/1
Question 2: is BW a mediator?

- We address the second question:
- by estimating the Natural Direct and Indirect Effects of $E$ on $Y$, where:
  - the indirect effect is made of (a)
  - and (b),
  - and the direct effect is (c):

![Diagram]

- $E ightarrow M ightarrow Y$
- $E ightarrow L ightarrow Y$
- $M ightarrow Y$
- $L ightarrow Y$
Question 2: is BW a mediator?

- We address the **second question**: by estimating the Natural Direct and Indirect Effects of $E$ on $Y$, where:
  - the **indirect effect** is made of (a)
  - and (b),
  - and the **direct effect** is (c):

![Diagram](image)
We address the second question:

by estimating the Natural Direct and Indirect Effects of \( E \) on \( Y \), where:

- the indirect effect is made of (a)
- and (b),
- and the direct effect is (c):

\[
\text{MW}^\land E L Y
\]
Estimands (CDE(m) and PNDE, TNIE) are expressed as OR contrasts.

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

- No non-linearities in $L$: Model II (Petersen et al., 2006).

Estimation:

- accounting for the estimation of $Pr(L = 1)$ and clustering of children.
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).

Estimation:

- via Monte Carlo G-computation (Daniel, et al., 2011),
- accounting for the estimation of $Pr(L = 1)$ and clustering of children.
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).

Estimation:

- accounting for the estimation of \( Pr(L = 1) \) and clustering of children.
The ONS 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.

- Today: data restricted to births of white mothers (85%), with complete information on maternal education (loss of 3.8%).
The ONS 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.
- Today: data restricted to births of white mothers (85%), with complete information on maternal education (loss of 3.8%).
The study population

  - **E**: 38% of mother with fewer than 5 O-levels (“Low education”).
  - **M**: 5.3% with birth weight < 2.5kg.
  - **Y**: 0.54% (862) infant deaths.
  - Mortality rates vary greatly by BW, moderately by sex, improving with calendar time:
The study population

- **E**: 38% of mother with fewer that 5 O-levels ("Low education").
- **M**: 5.3% with birth weight < 2.5kg.
- **Y**: 0.54% (862) infant deaths.
- Mortality rates vary greatly by BW, moderately by sex, improving with calendar time:
The study population

- **E**: 38% of mother with fewer that 5 O-levels (“Low education”).
- **M**: 5.3% with birth weight < 2.5kg.
- **Y**: 0.54% (862) infant deaths.
- Mortality rates vary greatly by BW, moderately by sex, improving with calendar time:
The study population

- **E**: 38% of mother with fewer that 5 O-levels ("Low education").
- **M**: 5.3% with birth weight < 2.5kg.
- **Y**: 0.54% (862) infant deaths.

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

- **E**: 38% of mother with fewer than 5 O-levels ("Low education").
- **M**: 5.3% with birth weight < 2.5kg.
- **Y**: 0.54% (862) infant deaths.
- Mortality rates vary greatly by BW, moderately by sex, improving with calendar time:

![Graph showing infant death rates by birth weight deciles and sex.](image-url)
Natural direct and indirect effects of low maternal education

VERY PRELIMINARY RESULTS - SEs not yet corrected

<table>
<thead>
<tr>
<th></th>
<th>Model I</th>
<th></th>
<th>Model II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ln OR</td>
<td>(SE)</td>
<td>ln OR</td>
</tr>
<tr>
<td>CDE(0)</td>
<td>–</td>
<td>–</td>
<td>0.205</td>
</tr>
<tr>
<td>CDE(1)</td>
<td>–</td>
<td>–</td>
<td>0.206</td>
</tr>
<tr>
<td>PNDE</td>
<td>0.221</td>
<td>(0.082)</td>
<td>0.227</td>
</tr>
<tr>
<td>TNIE</td>
<td>0.011</td>
<td>(0.007)</td>
<td>-0.012</td>
</tr>
<tr>
<td>TCE</td>
<td>0.232</td>
<td>(0.082)</td>
<td>0.205</td>
</tr>
</tbody>
</table>

- 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.
- There is little support for a mediating effect of BW (also supported by sensitivity analyses).
- However, problems of stability of the results.
**Natural direct and indirect effects of low maternal education**

**VERY PRELIMINARY RESULTS - SEs not yet corrected**

<table>
<thead>
<tr>
<th></th>
<th>Model I</th>
<th>Model II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ln OR (SE)</td>
<td>ln OR (SE)</td>
</tr>
<tr>
<td>CDE(0)</td>
<td>– – 0.205 (0.076)</td>
<td>0.205 (0.076)</td>
</tr>
<tr>
<td>CDE(1)</td>
<td>– – 0.206 (0.076)</td>
<td>0.206 (0.076)</td>
</tr>
<tr>
<td>PNDE</td>
<td>0.221 (0.082)</td>
<td>0.227 (0.077)</td>
</tr>
<tr>
<td>TNIE</td>
<td>0.011 (0.007)</td>
<td>-0.012 (0.005)</td>
</tr>
<tr>
<td>TCE</td>
<td>0.232 (0.082)</td>
<td>0.205 (0.076)</td>
</tr>
</tbody>
</table>

- 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.
- There is little support for a mediating effect of BW (also supported by sensitivity analyses).
- However problems of stability of the results.
What about unmeasured confounders?

- Results would still be biased.
- However, not if $U_1$ and $U_2$ influenced $L$ directly.
What about unmeasured confounders?

- Results would still be biased.
- However, not if $U_1$ and $U_2$ influenced $L$ directly.
Conclusions

- Approach may contribute to the debate about the BW paradox by representing the underlying biological process via a latent variable.

- Results depend 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.

- These are being addressed by extending the Monte Carlo G-formula algorithm.
Conclusions

- Approach may contribute to the debate about the BW paradox by representing the underlying biological process via a latent variable.

- Results depend 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.

- These are being addressed by extending the Monte Carlo G-formula algorithm.
Conclusions

- Approach may contribute to the debate about the BW paradox by representing the underlying biological process via a latent variable.

- Results depend 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.

- These are being addressed by extending the Monte Carlo G-formula algorithm.
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.

- These are being addressed by extending the Monte Carlo G-formula algorithm.
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.

Census output is Crown copyright and is reproduced with the permission of the Controller of HMSO and the Queen’s Printer for Scotland.
References

- Yerushalmy, J. Mother’s cigarette smoking and survival of infant. AJOG 1964;88:505-518.
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

<table>
<thead>
<tr>
<th>Mat Education</th>
<th>Birth weight ≥ 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>92,704</td>
<td>59,141</td>
</tr>
<tr>
<td>Deaths</td>
<td>220</td>
<td>222</td>
</tr>
<tr>
<td>Rates (x 1,000)</td>
<td>2.4</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Sex-adjusted OR

|                   | 1.58 (1.31, 1.91) | 0.92 (0.76, 1.12) |
|                   | (0.031)           |                    |

Adjusted OR

|                   | 1.23 (1.01, 1.49) | 0.92 (0.76, 1.12) |
|                   | (0.036)           |                    |
### The Wilcox model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Class 1</th>
<th>Class 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For $\mu$</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>3.51</td>
<td>3.65</td>
</tr>
<tr>
<td>sex</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>year birth</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>mat age</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>birth order</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>For $\sigma$</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.90</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>For $\pi$</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sex</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mat educ</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Only Infant deaths</th>
<th>Only Infant deaths &amp; Still births</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model I</td>
<td>Model II</td>
</tr>
<tr>
<td><strong>ln OR</strong></td>
<td><strong>(SE)</strong></td>
<td><strong>ln OR</strong></td>
</tr>
<tr>
<td><strong>PNDE</strong></td>
<td>0.221 (0.082)</td>
<td>0.174 (0.067)</td>
</tr>
<tr>
<td><strong>TNIE</strong></td>
<td>0.011 (0.007)</td>
<td>0.018 (0.008)</td>
</tr>
<tr>
<td><strong>TCE</strong></td>
<td>0.232 (0.082)</td>
<td>0.192 (0.066)</td>
</tr>
</tbody>
</table>