The social gradient in birthweight at term: quantification of the mediating role of maternal smoking and body mass index

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BACKGROUND: Maternal education is associated with the birthweight of offspring. We sought to quantify the role of maternal body mass index (BMI) and smoking as intermediary variables between maternal education and birthweight at term.

METHODS: We examined the association between maternal education, BMI, smoking and offspring’s birthweight among women who delivered at term in the Danish National Birth Cohort (n = 75,085).

RESULTS: Compared with mothers with more than 12 years of education, women with 10–12 years of education had babies that were 12 (4–19) g lighter. Mothers with 9 years of education had babies that were 51 (95% CI; 39–62) g lighter. BMI and smoking affected the association between maternal education and birthweight, albeit in different directions. If all mothers had the BMI of the highest educated mothers, the deficits would be larger: 20 (−22 to −19) and 74 (−80 to −68) g, respectively. If all mothers smoked like the highest educated mothers, mothers with a shorter education would have the heaviest babies: the difference would be 9 (2–16) and 23 (11–36) g, respectively. In combination, smoking and BMI all but explained the educational gradient in birthweight at term.

CONCLUSION: Maternal smoking and BMI are important intermediates of the educational gradient in birthweight at term. As the prevalence of smoking is dropping and the prevalence of obesity is increasing the educational gradient will likely reverse, but it seems unlikely that this will translate into a health advantage for the children of the least educated mothers.

Key words: birthweight / smoking / body mass index / socioeconomic factors / cohort study

Introduction

Birthweight is a predictor of a person’s health trajectory over the life-course, and low birthweight (LBW) (<2500 g) is consequently one of the indicators of health that is monitored globally by the World Health Organization even though the value of LBW as an outcome has been questioned (Adams et al., 2003; World Health Organization, 2005). Babies that are born light are at increased risk of dying throughout the neonatal period compared with normal weight babies (Wilcox et al., 1995). Following Barker’s seminal work on birthweight and health in adulthood, birthweight has been associated with a host of diseases in adulthood, including diabetes, stroke and coronary heart disease (Barker, 1998; Osler et al., 2003; Andersen and Osler, 2004; Huxley et al., 2007; Baker et al., 2008). Some of this research has been contested (Wilcox, 2001; Basso et al., 2006; Hernandez-Diaz et al., 2006), but studies of using twin- and sibling-designs have suggested that birthweight has a causal effect on long-run health outcomes (Hubinette et al., 2001; Nilsson et al., 2005; Black et al., 2007; Hultman et al., 2007; Johansson et al., 2008; Bergvall and Cnattingius, 2008).

Numerous studies have documented an inverse association between different measures of socioeconomic position (SEP) and birthweight in many different populations, including the Nordic populations (Gissler et al., 2003; Mortensen et al., 2008). The role of smoking as a mediator of this association has been examined in several studies, but only relatively few studies have examined role of
body mass index (BMI) in the relationship between SEP and birthweight. In combination, these two factors are particularly interesting for several reasons. Firstly, the prevalence of obesity is increasing whereas the prevalence of smoking is decreasing. Secondly, both BMI and smoking are related to SEP, but in ways that affect the social gradient in birthweight differently. Smoking is related to low SEP and decreases birthweight, a high BMI is related to low SEP and increases birthweight.

The aim of this present study is to examine how the association between maternal education and birthweight is mediated by maternal BMI and smoking.

Materials and Methods

Population and study design

This study was carried out in the Danish National Birth Cohort (DNBC), which is a nationwide study of pregnant women and their offspring. The women were recruited early in pregnancy in the period 1996–2002. A total of 100,418 pregnant women, who returned a consent form, were included in the study. Information on exposures during the pregnancy were assessed in two computer-assisted phone interviews scheduled to take place in the 12th to 16th week and in the 30th week of pregnancy. The DNBC has been described in further detail elsewhere (Olsen et al., 2001).

For this present study, we first excluded women who could not be linked with registries (n = 124). The remaining 100,294 pregnancies resulted in 94,670 live births. Of these, 83,149 were to participants of the first and second interview. Finally, we excluded post- and preterm births (n = 45,666) and women with missing information on variables of interest (n = 3498), leaving the analytic sample at 75,085 births. Of these births, 7214 had an older sibling in the cohort. The births excluded due to non-participation in the first and second interview had lower mean birthweights (51 g lighter in the 40th completed week of gestation, P < 0.001) and had on average lower educational attainment (χ²-test: P < 0.001). The births excluded due to missing values on covariates, were much lighter (130 g lighter in the 40th completed week of gestation, P < 0.001) and also had lower educational attainment (χ²-test: P = 0.001).

Variables

Through record linkage with the civil registration system we obtained information on highest completed maternal education in the year preceding birth of the offspring from the ‘Integrated Database for Labor Market Research’ Information. Maternal education was classified in three groups according to length of education: 9 years or less (preprimary, primary and lower secondary), 10–12 years (upper secondary, post-secondary non-tertiary education), 13 years or more (tertiary).

At the two interviews, conducted on average at the 17th and 32th week of pregnancy, the women were asked if they smoked. If they smoked, they were asked what they smoked (cigarettes, pipe, cigars) and how much on average they had been smoking during pregnancy. From this information, we calculated the average number of cigarettes-per-day equivalent units and classified the women as non-smokers (0 units), moderate smokers (0 < units < 10) and heavy smokers (10 ≤ units). At the first interview, the women were also asked if their spouse or partner smoked (daily smoker, less than daily smoker, non-smoker). Also assessed during the first interview, maternal prepregnant BMI (kg/m²) was calculated from self-reported height and weight and divided into five categories: Underweight (BMI < 18.5), normal weight (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 30), obese (30 ≤ BMI < 35) and obese class II or higher (BMI ≥ 35). Maternal country of birth—a proxy for ethnicity—was coded into a four-category variable (Denmark, other Nordic country, other Organization for Economic Cooperation and Development (OECD) country, rest of the world). Year of birth of the mother was recoded into five groups (<1965, 1965–1969, 1970–1974, 1975–1979, <1980). Maternal height—a proxy for growth and environmental influences in childhood—was coded in three categories (<160, 160–170, >170 cm). Information on medical parity (not including current pregnancy) was gathered from the Medical Birth Registry and was recoded into four groups (0, 1, 2, ≥3). Maternal age was coded into a five-category variable (age ≤ 25, 25 < age ≤ 30, 30 < age ≤ 35, 35 < age ≤ 40, age > 40).

Information on birthweight and length of gestation was taken from the Danish Medical Birth Registry by linkage with the mother’s civil registration number. According to national guidelines, length of gestation was estimated using information on the first day of the last menstrual period (among women with a regular bleeding pattern during the last 3 months before pregnancy) or from an ultrasound examination carried out before the 24th week of gestation. Birthweight is affected by length of gestation and fetal growth; to take account of the effect of gestational age on birthweight, we restricted our analyses to term births (37–42 completed weeks) and adjusted all analyses for gestational age (in completed weeks).

Statistical analysis

The Directed Acyclic Graph (DAG) presented in Fig. 1 was constructed by having three epidemiologists construct the DAG independently. The epidemiologists were instructed to draw a DAG of maternal smoking, maternal prepregnant BMI and birthweight without consideration of the data available. The resulting DAGs were then reviewed and synthesized by the first and last author. The resulting DAG is a quantification of the authors’ subjective beliefs and should not be considered as a ‘true’ model of the causal relationships, but rather as one model among other possible models. The DAG predicts that, conditional on confounders and education, BMI and smoking should be independent of each other (i.e. BMI and smoking should be d-separated by education and the confounders). To test this, we calculated Cochran Mantel–Haenzel tests of conditional independence.

For the analyses of mediation, we decomposed the total effect (TE) into a direct effect and an indirect effect. Commonly, the strategy of decomposition is only used when there is no (unit-level) interaction between exposure and outcome (Robins and Greenland, 1992; Kaufman et al., 2004). Statistical interaction is a phenomenon that is dependent on the

![Figure 1](https://example.com/figure1.png)
The social gradients in birthweight at term: mediation by smoking and BMI

We note that (3) does not hold for non-linear models, e.g. logistic distribution under no exposure. In our case, this corresponds to calculating other level and the mediator in the exposed is fixed at its (counterfactual) in outcome when exposure is changed from the reference level to some other level. The weights of

\[ \text{NDE}(x, x^*; Y) = E(Y_{x, X^*}) - E(Y_{x^*, X^*}) \]

where \( Y \) is the outcome, \( x \) is some value of the exposure \( X \), \( x^* \) is the reference group of exposure \( X \). The NDE can be defined as

\[ \text{NDE}(x, x^*; Y) = E(Y_{x, X^*}) - E(Y_{x^*, X^*}) \]

where \( Y \) is the outcome, \( x \) is some value of the exposure \( X \), \( x^* \) is the reference group of exposure \( X \), and \( Z^* \) is the distribution of the mediator in the reference group of exposure \( X \). In other words, NDE is the change in outcome when exposure is changed from the reference level to some other level and the mediator in the exposed is fixed at its (counterfactual) distribution under no exposure. In our case, this corresponds to calculating the direct effect whereas fixing the intermediate variables at the distribution in the reference group (i.e. fixing mediator distribution, changing exposure).

The TIE is obtained by subtracting the NDE from the TE (Robins, 2002):

\[ \text{TIE}(x, x^*; Y) = \text{TE}(x, x^*; Y) - \text{NDE}(x, x^*; Y) \]

We note that (3) does not hold for non-linear models, e.g. logistic regression, as previously shown (Mackinnon et al., 2007). The NDEs are calculated as

\[ \text{NDE}(x, x^*; Y) = \sum_{z,w} [E(Y_{x,z|w}) - E(Y_{x^*,z|w})] P(Z^* = z|w)P(w) \]

where \( Y \) is the outcome, \( Z \) is the mediator, \( x \) is some value of the exposure \( X \), \( x^* \) is the reference group of exposure \( X \), and \( W \) is a set of confounders. \( E(Y_{x,z|w}) - E(Y_{x^*,z|w}) \) is estimated from a regression of \( Y \) on \( X, Z \) and \( W \) as described below. The weights of \( P(Z^* = z|w)P(w) \) were calculated by tabulating \( Z \) by \( X \) and \( W \).

The direct effect is identifiable if two assumptions are met: first, there has to be no unmeasured confounding of any pathway (Cole and Hernan, 2002). Secondly, level of the mediator(s) under no exposure has to be uninformative for the effect of the exposure at a controlled level of the mediator(s). The first assumption follows from standard epidemiological concepts of confounding. The second assumption is not testable because the counterfactual is not observed. If the direct effect assumption fails to hold, the estimand still addresses a question of interest because it provides a summary of the direct effect of the exposure in a population where the intermediate is controlled at its counterfactual distribution in the absence of exposure (Petersen et al., 2006).

The TE was estimated from a linear regression model that included education, ethnicity and the mother’s birth year/maternal age at the index pregnancy (i.e. the pregnancy at which the mother is included in the study), the mother’s height and gestational age in completed weeks. The direct and indirect effects were estimated from a model that additionally included BMI and/or smoking. To account for the fact that some mothers participated with more than one child, we used the general estimation equation (GEE) method with an independence working correlation in SAS PROC GENMOD to correct the standard errors. The estimates from the GEE model had only marginally higher standard errors than the corresponding estimates estimated under the assumption of independence between observations. Bootstrapping (sampling with replacement, 5000 repeats) was used to derive confidence limits for direct and indirect effects.

Results

The proposed causal model is schematically represented as a DAG in Fig. 1. We propose that ethnicity, the mother’s birth year/maternal age at the index pregnancy and the mother’s height—used here as a proxy for growth and environmental influences in childhood—acts as confounders. The mother’s birth year/maternal age at the index pregnancy is represented by one variable in the analyses because they are collinear as the women were recruited over a short (7-year) time span. Ethnicity is closely associated with educational chances and birthweight at term. The mother’s year of birth/maternal age at the index pregnancy affects the chance of obtaining an education at the time of the index pregnancy and possibly also affects mediators and/or birthweight at term. It is known that smoking affects BMI, but we assumed that smoking in third trimester did not affect prepregnant BMI.

The DAG suggests that smoking and BMI should be marginally associated as they share common ancestors (education, height, ethnicity, mother’s birth year/maternal age), but independent conditional on these ancestors. This means that within strata of education and confounders, the BMI distribution of smokers and non-smokers should be similar (or that the smoking prevalence should be similar with categories of BMI). Smoking and BMI were marginally associated (Cochrane Mantel–Haenzel test of independence: \( P < 0.001 \)); among smokers, the proportion of pregnant women with a BMI < 18.5 and BMI ≥ 30 was slightly higher than among non-smokers (data not shown). There was some evidence against the DAG as smoking and BMI was still statistically significantly associated conditional on the ancestors (Cochrane Mantel–Haenzel test of independence: \( P < 0.001 \)). We examined the within-strata association for each of the four ancestor variables, and it seems that particularly the association within strata of education was stronger than expected although considerably weaker than the marginal association (data not shown).

Of the 75 085 births included in this study, 13% were born by women with an education of 9 years or less. Forty-nine (49%) of the children were born of mothers with 10–12 years of education, although 38% were born of mothers with 13 years or more of education. A graded association between maternal education and birthweight is evident in the crude data. The overall prevalence of smoking in the third trimester interview was 18%. Four percent (4%) of the mothers were underweight, 19% were overweight and 8% were obese. Smoking and BMI were associated with birthweight, albeit in different directions. Only a small proportion of the births (2%) in the cohort were to mothers of non-Danish origin. Parity, maternal age, year of birth and week of gestation of the infant were also associated with the outcomes (Table I).
Maternal education was strongly associated with smoking and BMI (Table II). It is also evident from Table II that smoking and high BMI tended to cluster within strata defined by maternal education.

Both smoking at the third trimester interview and BMI were strongly associated with birthweight at term independent of each other (Table III). Once smoking at the third trimester interview was taken into account, environmental smoking exposure (as measured by the partner or spouse’s smoking habits) or the mother’s smoking at the second trimester interview was associated with birthweight at term. However, the effect of smoking at the third trimester interview differed depending on the level of maternal education. The effect of light smoking was roughly twice as strong among the least educated

**Table I** Characteristics of 75,085 mothers, who gave birth to term live singleborns.

<table>
<thead>
<tr>
<th>Maternal characteristic</th>
<th>n</th>
<th>%</th>
<th>Offspring’s mean birthweight</th>
<th>P* for mean birthweight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 years or less</td>
<td>9469</td>
<td>12.6</td>
<td>3562</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>10–12 years</td>
<td>36,912</td>
<td>49.2</td>
<td>3635</td>
<td></td>
</tr>
<tr>
<td>13 or more years</td>
<td>28,704</td>
<td>38.3</td>
<td>3668</td>
<td></td>
</tr>
<tr>
<td>Smoking at interview in 32nd week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>61,879</td>
<td>82.4</td>
<td>3677</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Light smoker</td>
<td>7136</td>
<td>9.5</td>
<td>3502</td>
<td></td>
</tr>
<tr>
<td>Moderate/heavy smoker</td>
<td>6070</td>
<td>8.1</td>
<td>3400</td>
<td></td>
</tr>
<tr>
<td>Prepregnant BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 18.5</td>
<td>33,16</td>
<td>4.4</td>
<td>3423</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>18.5 ≤ BMI &lt; 25</td>
<td>51,060</td>
<td>68.0</td>
<td>3615</td>
<td></td>
</tr>
<tr>
<td>25 ≤ BMI &lt; 30</td>
<td>14,589</td>
<td>19.4</td>
<td>3714</td>
<td></td>
</tr>
<tr>
<td>30 ≤ BMI &lt; 35</td>
<td>4,461</td>
<td>5.9</td>
<td>3746</td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 35</td>
<td>1,659</td>
<td>2.2</td>
<td>3821</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danish</td>
<td>73,469</td>
<td>97.9</td>
<td>3639</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Other Nordic</td>
<td>448</td>
<td>0.6</td>
<td>3677</td>
<td></td>
</tr>
<tr>
<td>Other OECD</td>
<td>872</td>
<td>1.2</td>
<td>3607</td>
<td></td>
</tr>
<tr>
<td>Rest of the world</td>
<td>296</td>
<td>0.4</td>
<td>3488</td>
<td></td>
</tr>
<tr>
<td>Mother’s year of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth year &lt; 1965</td>
<td>5,861</td>
<td>7.8</td>
<td>3653</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>1965 ≤ birth year &lt; 1970</td>
<td>21,393</td>
<td>28.5</td>
<td>3672</td>
<td></td>
</tr>
<tr>
<td>1970 ≤ birth year &lt; 1975</td>
<td>31,741</td>
<td>41.8</td>
<td>3640</td>
<td></td>
</tr>
<tr>
<td>1975 ≤ birth year &lt; 1980</td>
<td>14,652</td>
<td>19.5</td>
<td>3594</td>
<td></td>
</tr>
<tr>
<td>Birth year ≥ 1980</td>
<td>1,808</td>
<td>2.4</td>
<td>3521</td>
<td></td>
</tr>
<tr>
<td>Maternal height</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 160 cm</td>
<td>7,406</td>
<td>9.9</td>
<td>3465</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>160 cm &lt; height ≤ 170 cm</td>
<td>33,033</td>
<td>44.0</td>
<td>3591</td>
<td></td>
</tr>
<tr>
<td>&gt; 170 cm</td>
<td>34,646</td>
<td>46.1</td>
<td>3720</td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37 completed weeks</td>
<td>3,227</td>
<td>4.3</td>
<td>3164</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>38 completed weeks</td>
<td>8,541</td>
<td>11.4</td>
<td>3367</td>
<td></td>
</tr>
<tr>
<td>39 completed weeks</td>
<td>16,979</td>
<td>22.6</td>
<td>3543</td>
<td></td>
</tr>
<tr>
<td>40 completed weeks</td>
<td>23,170</td>
<td>30.9</td>
<td>3680</td>
<td></td>
</tr>
<tr>
<td>41 completed weeks</td>
<td>16,388</td>
<td>21.8</td>
<td>3809</td>
<td></td>
</tr>
<tr>
<td>42 completed weeks</td>
<td>6,780</td>
<td>9.0</td>
<td>3891</td>
<td></td>
</tr>
</tbody>
</table>

*P-value for a log-likelihood test of equal mean birthweights.

**Table II** Association between maternal education, smoking and BMI among 75,085 mothers, who gave birth to term live singleborns.

<table>
<thead>
<tr>
<th>Maternal education</th>
<th>Maternal smoking at interview in 32nd week</th>
<th>Prepregnant BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-smoker (%)</td>
<td>Light smoker (%)</td>
</tr>
<tr>
<td>13 or more years (n = 28,704)</td>
<td>91.0</td>
<td>6.2</td>
</tr>
<tr>
<td>10–12 years (n = 36,912)</td>
<td>81.3</td>
<td>10.3</td>
</tr>
<tr>
<td>9 years or less (n = 9,469)</td>
<td>60.6</td>
<td>16.4</td>
</tr>
</tbody>
</table>

Maternal education was strongly associated with smoking and BMI (Table II). It is also evident from Table II that smoking and high BMI tended to cluster within strata defined by maternal education.

Both smoking at the third trimester interview and BMI were strongly associated with birthweight at term independent of each other (Table III). Once smoking at the third trimester interview was taken into account, environmental smoking exposure (as measured by the partner or spouse’s smoking habits) or the mother’s smoking at the second trimester interview was associated with birthweight at term. However, the effect of smoking at the third trimester interview differed depending on the level of maternal education. The effect of light smoking was roughly twice as strong among the least educated
Maternal education, smoking and BMI in relation to birthweight at term (g) among 75 085 mothers, who gave birth to term live singleborns.

<table>
<thead>
<tr>
<th>Education</th>
<th>Crude</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 or more years</td>
<td>0 (reference)</td>
<td>0 (reference)</td>
</tr>
<tr>
<td>10–12 years</td>
<td>–29 (–36, –21)</td>
<td>–12 (–19, –4)</td>
</tr>
<tr>
<td>9 years or less</td>
<td>–89 (–100, –79)</td>
<td>–51 (–62, –39)</td>
</tr>
</tbody>
</table>

Smoking (Education: 13 or more years)
- Non-smoker          | 0 (reference)          | 0 (reference)         |

Smoking (Education: 10–12 years)
- Non-smoker          | 0 (reference)          | 0 (reference)         |
- Light smoker        | –163 (–180, –147)      | –162 (–178, –146)    |

Smoking (Education: 9 years or less)
- Non-smoker          | 0 (reference)          | 0 (reference)         |
- Moderate/heavy smoker| –290 (–314, –266)      | –288 (–312, –264)    |

BMI
- BMI < 18.5          | –193 (–210, –175)      | –181 (–198, –164)    |
- 18.5 ≤ BMI < 25     | 0 (reference)          | 0 (reference)         |
- 25 ≤ BMI < 30       | 98 (89, 107)           | 109 (100, 118)       |
- 30 ≤ BMI < 35       | 130 (115, 145)         | 154 (139, 169)       |
- BMI ≥ 35            | 205 (181, 230)         | 232 (208, 256)       |

All main effects and the interaction between education and smoking are statistically significant at an alpha-level of 0.001.

*Estimates are adjusted for ethnicity, mother’s year of birth, mother’s height, gestational age, and maternal education, smoking and BMI as appropriate.

Total, direct and indirect natural effects of maternal education on birthweight at term (g) among 75 085 mothers, who gave birth to term live singleborns.

<table>
<thead>
<tr>
<th>Total effect of education</th>
<th>Mediator(s): smoking</th>
<th>Mediator(s): BMI</th>
<th>Mediator(s): smoking and BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct effect of education</td>
<td>Smoking-mediated</td>
<td>Direct effect of education</td>
<td>BMI-mediated</td>
</tr>
</tbody>
</table>

Education
- 13 or more years
  - 0 (reference)          | 0 (reference)         | 0 (reference)         | 0 (reference)         |
- 10–12 years              | –12 (–19, –4)         | 9 (2, 16)           | –20 (–22, –19)        |
- 9 years or less          | –51 (–62, –39)        | 23 (11, 36)         | –74 (–80, –68)        |

Women by 14 g (12–16 g). The corresponding effect of smoking was a decrease of 74 g (68–80 g). Again, the biggest indirect effect was observed when comparing the best and least education mothers. But relative to the TE, BMI was a much more important mediator than smoking in explaining the educational differences in birthweight at term between the highest educated mothers and mothers with an education of 10–12 years. In combination, smoking and BMI explained almost all of the difference in birthweight at term between mothers with different educational backgrounds. If all mothers had the smoking habits of the most educated mothers, the offspring of the least educated mothers would experience the highest birthweight at term. If all mothers had the BMI distribution of the most educated mothers, low education would be more strongly associated with decreased birthweight at term.
Discussion

This study shows that maternal smoking and BMI are important mediators of the educational gradient in birthweight at term: smoking explained a large part of the educational differences. BMI had a smaller mediating effect, which seems to exist across the educational gradient. Also, smoking and BMI had opposite effects on the educational gradient in birthweight at term: if all mothers had the BMI of the highest educated mothers, the educational differences would be larger. If all mothers smoked like the highest educated mothers, mothers with a shorter education would have the heaviest babies. This study also showed smoking to have differential effects across the educational groups.

The data used in this study comes from the DNBC, which is a large prospective cohort study. In addition, we partly used data gathered from national registries, which are not subject to the information biases associated with self-reports. There are several sources of bias in this study. As our naïve DAG explicitly shows, we assume no selection bias, no unobserved confounding and no measurement error on all variables. These assumptions, which are commonly implicitly assumed in epidemiological studies, are not fully met. A recent study of the DNBC has shown little or no bias from non-participation (Nohr et al., 2006), but the findings of this present study might be more sensitive to the known bias in the prevalence of smoking and BMI because the distribution of these factors are used in the estimation of the direct and indirect effects. Also, if misclassification of gestational age is dependent on the mother’s education, this would induce selection bias because only term births were included. Uncontrolled confounding of the results, including confounding by uncontrolled causal intermediates, such as diet or physical activity during pregnancy, are likely to bias the results. Our own analyses showed that BMI and smoking was conditionally dependent, which may be due to confounding or biases not described by the DAG. Misclassification of intermediary variables will likely bias the indirect effects towards null, which means that the importance of the mediators will be underestimated. Some bias due to this mechanism is likely present in this study. The interaction between smoking and maternal education observed in this study is likely in part explained by the crude categorization of the smoking variable, which might result in an interaction if the residual exposure to smoking within each category depends on maternal education. Another explanation of the interaction is education-dependent underreporting of smoking or smoking- and education-dependent residual confounding by unobserved variables. The results were also highly dependent on our choice of confounders. For example, if parity was included and maternal height omitted the TE increased 2-fold (data not shown). The increase was largely unexplained by smoking and BMI, which means that the proportion of the educational gradient explained by smoking and BMI was much lower when parity was included and maternal height omitted. This limitation is difficult to overcome when the exposure (education) is practically impossible to randomize. One solution would be to find a suitable natural experiment (Currie and Moretti, 2003).

Because of the interaction between maternal education and smoking, we based the estimation of the direct and indirect effect of maternal education on birthweight at term on the natural effects-approach. This approach enables us to test an interesting hypothesis; if the distributions of BMI and smoking within the lower strata of maternal education were the same as in the highest, what would the difference in birthweight at term be? The choice of reference group—in this case a maternal education of 13 years or more—is admittedly arbitrary, albeit defensible from the standpoint of social epidemiology which is interested in explaining the disparity in health that exists between the best off groups and the less well-off groups. However, the problem of choice of reference group is not a problem that is restricted to studies of mediation, but is a general problem in epidemiology when quantifying the effects of variables that do not have a natural reference category.

The mediating effect of smoking on the social gradient in birthweight has been reviewed by Kramer et al. who concluded that cigarette smoking is the most important risk factor for intrauterine growth retardation. Kramer et al. (2000) also conclude that maternal underweight and short stature explains part of the social inequality in intraterine growth. This present study confirms those previous findings, but we suggest that maternal overweight might become more important as the prevalence of this factor increases whereas cigarette smoking prevalence decreases.

In this present paper, we show smoking and maternal overweight to have opposite effects on birthweight at term. As the factors appear not to interact in determining birthweight at term, our results suggest that smoking and obesity might cancel out each other: for example, the expected birthweight at term of a child to a light smoking obese mother with an education of 9 year or less would be almost exactly the same as for a non-smoking normal-weight mother in the same educational group. This does not, however, imply that joint exposure to these factors is equally healthy as being exposed to neither. It only implies that whatever the effect of maternal smoking and obesity may have on later health of the offspring, this effect is not reflected in birthweight at term. This observation highlights a challenge in etiological studies of the health consequences of birthweight; separating the causal effect of maternal exposures on offspring health from the causal effect of birthweight on offspring health. As the prevalence of smoking is dropping and the prevalence of obesity is increasing the educational gradient will likely reverse, but it seems unlikely that this will translate into a health advantage for the children of the least educated mothers. We are curious as to see how birthweight, often conceptualized as an indicator of intraterine biological programming of future health, will predict future health for birth cohorts with a low prevalence of maternal smoking and a high prevalence of maternal obesity.

In conclusion then, maternal smoking and BMI are important mediators of the educational gradient in birthweight at term. Smoking is especially important in explaining the differences between the highest and lowest educated mother, although BMI has a smaller mediating effect, which seems to exist across the educational gradient. We have shown that smoking and BMI have opposite mediating effects on the educational gradient in birthweight at term; BMI decreases the TE, whereas smoking increases it. This study also shows smoking to have differential effects across the educational groups.

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