Are Early-Life Socioeconomic Conditions Directly Related to Birth Outcomes? Grandmaternal Education, Grandchild Birth Weight, and Associated Bias Analyses


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Grandmaternal education may be related to grandchild birth weight (GBW) through maternal early-life development; however, conventional regression models may be endogenously confounded. Alternative models employing explicit structural assumptions may provide incrementally clearer evidence. We used data from the US National Longitudinal Study of Adolescent to Adult Health (1995–2009; 1,681 mother-child pairs) to estimate "direct effects" of grandmaternal educational level (less than high school, high school diploma or equivalent, or college degree) at the time of the mother’s birth on GBW, adjusted for maternal life-course factors: maltreatment as a child, education and income as an adult, prepregnancy overweight, and prenatal smoking. Using conventional and marginal structural model (MSM) approaches, we estimated 54-g (95% confidence interval: −14.0, 122.1) and 87-g (95% confidence interval: 10.9, 162.5) higher GBWs per increase in educational level, respectively. The MSM allowed simultaneous mediation by and adjustment for prepregnancy overweight. Estimates were insensitive to alternate structural assumptions and mediator parameterizations. Bias analysis suggested that a single unmeasured confounder would have to have a strong influence on GBW (approximately 150 g) or be greatly imbalanced across exposure groups (approximately 25%) to completely explain the findings. Coupling an MSM with sensitivity analyses provides some evidence that maternal early-life socioeconomic environment is directly associated with offspring birth weight.

Abbreviations: Add Health, National Longitudinal Study of Adolescent to Adult Health; BMI, body mass index; CI, confidence interval; MSM, marginal structural model; SEM, structural equation model; SES, socioeconomic status.

Editor’s note: An invited commentary on this article appears on page 579, and the authors’ response appears on page 583.

Many mechanisms potentially link education to health across the life span (1) and intergenerationally (2). For example, grandmaternal education may be directly related to grandchild health through the early development of mothers, independent of maternal attained socioeconomic status (SES) (3). Specifically, lower maternal educational attainment may be associated with an adverse intrauterine environment, fetal organogenesis, and epigenetic programming (4–6). For females, such programming may lead to poorer adult metabolic capacity, adverse pregnancy outcomes, and lower birth weight for the third generation (6–9).

Studies investigating associations between grandparental education and grandchild birth weight are few, and the estimated direct effects are difficult to interpret (9, 10). One challenge is the interpretation of results from multivariable regression models which adjust for maternal life-course variables that may be endogenous confounders (11–13). For example, attained body mass index (BMI; weight (kg)/height (m)²) may be a metabolic consequence of intrauterine development and may mediate its
impact on adult outcomes (14). At the same time, BMI may confound adult risk factor–outcome relationships. Unlike conventional regression, marginal structural models (MSMs) may be used to explicitly model such relationships and provide clearer estimates of association (11–19). One recent study on the intergenerational transmission of education employed an MSM to control for child and grandchild schooling (19). Incorporation of sensitivity analyses for modeling assumptions and unmeasured confounding can further strengthen evidence (20–22).

Focusing on maternal early-life environment (6, 8), we estimated associations between grandmaternal education at the time of the mother’s birth and grandchild birth weight using several multivariable regression models adjusting for maternal life-course factors. We compared these estimates with those obtained from structural equation models (SEMs) and MSM approaches. We used sensitivity analyses to evaluate whether MSM estimates differed due to model parameterization, assumptions about causal structure, and/or unmeasured confounding.

**METHODS**

**Study setting**

We used data from the National Longitudinal Study of Adolescent to Adult Health (Add Health), a nationally representative US longitudinal study of grade 7–12 adolescents (approximate ages 12–18 years) that began in 1994 (n = 90,118). Detailed information on Add Health respondents, the sampling frame, weighting algorithms (23), and study protocols can be found on the study’s website (www.cpc.unc.edu/projects/addhealth/). Briefly, in-home interviews were conducted with a core subset of respondents (randomly selected within school and sex strata) along with a parent, during which information was collected on demographic factors, health, attitudes, behaviors, and environment. Additional respondents and parents were interviewed on the basis of ethnic minority status, having siblings in the study, and/or being black with at least 1 college-educated parent (n = 20,745 respondents). Respondents first interviewed in wave I were followed for up to 3 additional in-home interviews conducted in 1996 (wave II), 2001–2002 (wave III), and 2007–2008 (wave IV). During wave IV, a total of 15,701 respondents (80.3% of those eligible in wave I) were interviewed. To approximate the target population of US adolescents in grades 7–11 in 1994–1995, investigators derived a grand sampling weight accounting for clustered sampling, attrition, and oversampling (23). Research on these data has been approved by the Institutional Review Board of the University of Washington (Seattle, Washington).

**Study population**

Respondents (G1—“mother”) were eligible for the current study if they were women, had a biological mother (G0—“grandmother”) who was interviewed during wave I, participated in both the wave I and wave IV interviews, and had at least 1 livebirth (G2—“grandchild”) during the course of the study. Since firstborn offspring are hypothesized to be more susceptible to adverse in utero programming from maternal constraint (24), we matched G1s to their first reported singleton birth (G2). There were 2,352 women who met the eligibility criteria. After excluding 48 (2.0%) respondents missing a recorded exposure status and 416 (18.0%) respondents missing a wave IV grand sampling weight because of missing wave II/III interviews, and 12 (0.5%) respondents missing both, we included 1,876 G1-G2 pairs in the current study. Women with missing sampling weights did not differ substantially from the analytical population (see Web Table 1, available at http://aje.oxfordjournals.org/).

**Measures**

**Primary exposure and outcome.** During wave I (1994–1995), a respondent’s mother (G0) was asked, “How far did you go in school?” Responses were coded into 3 categories: less than high school diploma, high school diploma or equivalent (e.g., General Educational Development certificate), or completed college degree. Because we were interested in G1s’ intrauterine experiences, we capped completed education at a high school diploma if G0 gave birth at or prior to age 21 years (n = 86). G2 birth weight (grams) was reported by G1 during the wave IV interview. When compared with birth records, maternal recall of child birth weight is fairly accurate (9).

**G1 psychosocial and socioeconomic stress mediators.** Childhood maltreatment (25) and adult SES (26) are important psychosocial stressors in G1s’ life course that may lie within the causal pathway between G0 education and G2 birth weight. In line with previous investigations in Add Health (25), we used self-reported incidents of neglect, physical abuse, and sexual abuse prior to 18 years of age to construct a maltreatment factor score. Factor scores were generated using principle-component factor analysis and quartimin rotations. Adult SES closest to the time of G2’s birth was measured using 3 variables: 1) self-reported total household income (dollars) during wave IV or one of the following approximations, based on the midpoint of categorical choices (capped at $100,000): $5,000, $12,500, $17,500, $25,000, $35,000, $45,000, $62,500, or $100,000; 2) attained education, categorized by last grade or schooling type completed; and 3) an indicator of whether G1 reported that she would be in debt in response to the following question: “Suppose you and others in your household were to sell all of your major possessions (including your home), turn all of your investments and other assets into cash, and pay off all of your debts. Would you have something left over, break even, or be in debt?” A factor score for adult SES was predicted as described above. If the respondent gave birth to G2 prior to 2001, a wave III factor score was calculated excluding the debt measure, not asked about in wave III. Correlations between the 2 SES factor scores were moderate (unadjusted Pearson’s r = 0.578; n = 1,665). Maltreatment and adult SES factor scores were also dichotomized at their median values (high/low; 19% had discordant wave III and wave IV SES categories).

**G1 biological and behavioral mediators.** Higher prepregnancy BMI is associated with lower maternal education and higher birth weights and may be a consequence of early-life programming (27, 28). G1 prepregnancy BMI was calculated...
from weight and height measures obtained by either wave II self-report, if G1 gave birth prior to or during 2001 (35% of births), or wave III study staff. Correlation between the 2 BMI measures was high (unadjusted Pearson’s r = 0.76; P < 0.0001), and past findings suggest that such self-reports may be reasonably accurate (29). Prepregnancy overweight status was defined as a BMI of 25 or more. Prenatal smoking is associated with maternal education and lower birth weight (27, 28, 30). We coded G1 prenatal smoking as any or none, based on self-reported smoking during the index pregnancy.

**Time-invariant confounders.** G0 age at G1’s birth is related to G0 educational attainment and may influence child-rearing practices and therefore the life-course psychosocial and biological stressors experienced by G1 (31, 32). Similarly, G0 self-reported race is related to G0 educational opportunity and attainment, as well as stressors experienced by G1 (33, 34). G0 race was coded as non-Hispanic white, Hispanic white, black (any ethnicity), or other nonwhite, with persons who reported any mixed race not including black being accorded the last category. Both variables were included as confounders in all analyses.

**Statistical analysis**

We examined the possibility that early-life SES may be associated with future pregnancy outcome (Figure 1) using 3 modeling approaches to estimate the direct effect of grandmaternal (G0) educational category (X) on the birth weight (Y) of her daughter’s (G1) child (G2), including any “developmental programming” pathway mediated through G1 prepregnancy overweight (O): 1) covariate-adjusted linear regression models of measured predictors of G2 birth weight, 2) a linear SEM using dichotomous mediators, and 3) a linear MSM using dichotomous mediators estimated by inverse probability weights. Using each approach, we attempted to account for time-invariant confounding by G0 age at G1’s birth (G) and G0 self-reported race (R), as well as endogenous confounding by G1 life-course mediators: a high level of childhood maltreatment prior to age 18 years (M), prepregnancy overweight (O), low adult SES (A), and any prenatal smoking (S). Finally, we tested vulnerability to certain model assumptions through sensitivity analyses.

**Covariate-adjusted linear regression.** Under this approach, it is impossible to estimate an effect of X on Y, while simultaneously controlling for mediator-outcome confounding by G1 prepregnancy overweight or obesity status (O). Instead, we fitted 2 separate multivariable linear regression models including exposure, confounders, and life-course mediators as predictors of G2 birth weight, including (model 1) and excluding (model 2) adjustment for O:

\[
E[Y_i | X_i = x, R_i = r, G_i = g, M_i = m, O_i = o, A_i = a, S_i = s] = \beta_0 + \beta_1 x + \beta_2 r + \beta_3 g + \beta_4 m + \beta_5 o + \beta_6 a + \beta_7 s. \quad (1)
\]

\[
E[Y_i | X_i = x, R_i = r, G_i = g, M_i = m, A_i = a, S_i = s] = \beta_0 + \beta_1 x + \beta_2 r + \beta_3 g + \beta_4 m + \beta_5 a + \beta_6 s. \quad (2)
\]

Neither model 1 (equation 1) nor model 2 (equation 2) can estimate our desired quantity: Model 1 would overadjust by removing the effect of X on Y mediated through O, and model 2 does not adequately control for A_i − Y_i or S_i − Y_i confounding by O. We used these models to compare different covariate functional forms and multiple imputation estimates.

**Structural equation model.** We next estimated direct and indirect effects of G0 education by fitting an SEM of our hypothesized causal structure using dichotomous forms of our mediators (Figure 2). Unlike multivariable regression, it is possible to model the effect of G0 education on G2 birth weight and the mediated effect through G1 prepregnancy overweight.

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**Figure 1.** Causal diagram of hypothesized life-course determinants of birth weight in the National Longitudinal Study of Adolescent to Adult Health, United States, 1995–2009. Each exposure and mediator is assumed to have an effect on all other mediators that arise subsequent to it. Directed edges are drawn with different patterns based on their source for visual effect only; they do not reflect any additional knowledge or specification about relationships. Letters in parentheses correspond to the variable names in the fitted models (see text), with the exception of G0 confounders (C), which represents a vector of grandmother’s (G0) age at the daughter’s/respondent’s (G1’s) birth (G) and G0 race (R). The effect of interest is the controlled direct effect of G0 education (X) on grandchild (G2) birth weight (Y), including the pathway mediated through prepregnancy overweight (O). Abbreviation: SES, socioeconomic status.
if the SEM is correctly specified. We used the SEM to qualitatively verify our causal structure and as a reference for sensitivity analyses.

**MSM estimated by inverse probability weighting.** Finally, we tested the controlled direct effect of G0 education \((X_i)\) on G2 birth weight \((Y_i)\) by fitting the following regression model (model 3):

\[
E[Y_i|X_i = x, M_i = m, A_i = a, S_i = s] = \beta_0 + \beta_1 x + \beta_2 m + \beta_3 a + \beta_5 s.
\]  

(3)

weighting individual subjects by the inverse probability of their exposure to their given stratum of G0 education and the dichotomous mediators. Stabilized inverse probability weights (35) for G0 education \((w_i^X)\) were estimated by multinomial logistic regression to predict the probability for a given stratum of G0 education given a vector of \(C\) confounders. Stabilized inverse probability weights for mediators were calculated using logistic regression, giving regard to temporality (Figure 1):

G0 education:

\[
w_i^X = \frac{P(X = x_i)}{P(X = x_i|C = c_i)}.
\]  

(4)

Childhood maltreatment:

\[
w_i^M = \frac{P(M = m_i|C = c_i)}{P(M = m_i|X = x_i, C = c_i)}.
\]  

(5)

Adult SES:

\[
w_i^A = \frac{P(A = a_i|C = c_i)}{P(A = a_i|X = x_i, M = m_i, O = o_i, C = c_i)}.
\]  

(6)

Prenatal smoking:

\[
w_i^S = \frac{P(S = s_i|C = c_i)}{P(S = s_i|X = x_i, M = m_i, O = o_i, A = a_i, C = c_i)}.
\]  

(7)

Note that variables for controlling confounding by G0 race and age (collectively, the vector \(C\)) do not appear directly in model 3 but rather are controlled indirectly by including \(C\) in the weighting equations (equations 4–7). \(O\) is excluded in model 3, allowing the mediated path to be included in the controlled direct effect.

To account for the survey design and produce correct standard errors (23), we estimated each weight with the svy option in Stata (StataCorp LP, College Station, Texas) after using the wave IV grand sampling weights \((w_i^{gsw})\), clustering, and stratification variables for the svyset command in Stata. An overall weight \((W_{overall})\) was then generated for each subject using the product of the stabilized weights and \(w_i^{gsw}:

Overall weight:

\[
W_{overall} = w_i^X \times w_i^M \times w_i^A \times w_i^S \times w_i^{gsw}.
\]  

(8)

The svy option was subsequently used to fit model 3 using \(W_{overall}\) for the svyset command. An analogous method was described by Brumback et al. (36) for SAS (SAS Institute Inc., Cary, North Carolina). No interaction terms were included in these analyses, as there was not consistent evidence of additive mediator-exposure interactions.

Past literature has outlined important assumptions required to identify controlled direct effects using inverse probability weight estimators (12, 13). We evaluated the potential violations of the positivity assumption through the production

**Figure 2.** Structural equation model of life-course determinants of birth weight with unstandardized coefficients, National Longitudinal Study of Adolescent to Adult Health, United States, 1995–2009. For clarity, solid edges denote statistically significant associations \((*P < 0.05; **P < 0.005)\). For these associations, unstandardized point estimates are also provided. G0, generation 0 (grandmother); G1, generation 1 (mother/respondent); G2, generation 2 (grandchild); SES, socioeconomic status.
of contingency tables, crossing each exposure and mediator by category of predictor, graphing distributions of weights, and searching for small predicted probabilities (37). We found little evidence for violations of positivity (Web Tables 2–4; Web Figure 1). In addition, to address the validity of our model on the basis of prior knowledge and temporal sequence and assumptions regarding no unmeasured exposure- and mediator-outcome confounding, we conducted several sensitivity analyses.

Sensitivity analyses

Model specification. Preterm birth is an important mediator of low birth weight and may be of great interest (38, 39). We refitted model 3 after adding an indicator for birth before 37 weeks’ gestation and a corresponding probability weight. Additionally, we examined the sensitivity of model 3 to: 1) truncating weights at the 1st/99th, 5th/95th, and 10th/90th percentiles to evaluate the influence of rare treatment types (37); 2) including interaction terms in the estimation of weights (equations 4–7); and 3) reversing the presumed temporal relationship of adult SES and prepregnancy overweight by removing $O$ from equation 6.

Data replacement. To analyze the sensitivity of our analysis to mediator values missing at random conditional on available data, we refitted models 1 and 2 using multiple imputation by chained equations (40). For model 3, sensitivity to missingness was assessed by replacing missing values for G1 mediators and reweighting. Three strategies were used for replacement: First, all missing values were assumed to be indicative of risk (i.e., missing values for adult SES were replaced with an indicator of low adult SES); second, missing values for wave III prepregnancy overweight and wave IV adult SES were replaced with their values from waves II and III, respectively; and third, all values for these 2 mediators were replaced with their values from waves II and III, respectively.

Table 1.

<table>
<thead>
<tr>
<th>Generation and Characteristic</th>
<th>Total (n = 1,681)</th>
<th>Less Than High School Diploma (n = 345)</th>
<th>High School Diploma or Equivalent (n = 1,064)</th>
<th>College Degree or Higher (n = 272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% No. Mean (SD)</td>
<td>% No. Mean (SD)</td>
<td>% No. Mean (SD)</td>
<td>% No. Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>G0 (grandmother)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white race</td>
<td>62 1,033</td>
<td>46 160</td>
<td>66 706</td>
<td>61 167</td>
</tr>
<tr>
<td>Age at G1’s birth, years</td>
<td>24.8 (5.2)</td>
<td>24.2 (5.9)</td>
<td>24.7 (5.1)</td>
<td>26.1 (4.8)</td>
</tr>
<tr>
<td>G1 (mother)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood maltreatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever neglected</td>
<td>50 840</td>
<td>49 169</td>
<td>51 537</td>
<td>49 134</td>
</tr>
<tr>
<td>Ever physically abused</td>
<td>18 304</td>
<td>20 70</td>
<td>18 188</td>
<td>17 46</td>
</tr>
<tr>
<td>Ever sexually abused</td>
<td>8 136</td>
<td>8 28</td>
<td>8 85</td>
<td>9 23</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wave II</td>
<td>22.7 (4.5)</td>
<td>23.3 (4.5)</td>
<td>22.6 (4.5)</td>
<td>22.0 (4.2)</td>
</tr>
<tr>
<td>Wave III</td>
<td>26.7 (6.7)</td>
<td>27.4 (6.8)</td>
<td>26.6 (6.6)</td>
<td>26.0 (7.0)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>88 1,486</td>
<td>79 274</td>
<td>89 951</td>
<td>96 261</td>
</tr>
<tr>
<td>In debt</td>
<td>22 375</td>
<td>24 81</td>
<td>22 231</td>
<td>23 63</td>
</tr>
<tr>
<td>Average annual household income, 2008 dollars</td>
<td>58,842 (41,878)</td>
<td>47,681 (31,895)</td>
<td>58,761 (42,601)</td>
<td>72,880 (45,670)</td>
</tr>
<tr>
<td>Any prenatal smoking</td>
<td>19 325</td>
<td>19 66</td>
<td>21 222</td>
<td>14 37</td>
</tr>
<tr>
<td>G2 (offspring)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>39.1 (2.4)</td>
<td>39.2 (2.1)</td>
<td>39.1 (2.5)</td>
<td>38.9 (2.2)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>9 155</td>
<td>9 31</td>
<td>9 100</td>
<td>9 24</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3,265 (611)</td>
<td>3,220 (579)</td>
<td>3,268 (623)</td>
<td>3,309 (602)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>9 156</td>
<td>9 31</td>
<td>9 100</td>
<td>9 25</td>
</tr>
</tbody>
</table>

Abbreviations: G0, generation 0 (grandmother); G1, generation 1 (mother/respondent); G2, generation 2 (grandchild); SD, standard deviation.

a Mean values, SDs, and percentages presented here correspond to those of the sample (i.e., without survey weighting).
b Weight (kg)/height (m)$^2$.
c The combined income of G1 and her spouse/partner or G1 and her family. If an individual responded by selecting an income category, she was assigned the mean value of the category (i.e., "$5,000–$9,999" = $7,500).
d Based on the question, "How many weeks early or late was your baby born?" with "on time" being interpreted as 40 weeks.
e Estimated as gestational age <37 weeks, based on the above question.
f Reported birth weight <2,500 g.
Quantitative bias analysis. To assess the robustness of model 3 to unmeasured confounding, we simulated the influence of a hypothetical binary mediator-outcome confounder (22, 41). Assuming an unmeasured binary confounder \( U \) with no effect modification by \( G_0 \) education, we specified ranges for 2 sensitivity parameters \( g \) and \( d \), with \( g \) corresponding to the effect of \( U \) on \( G_2 \) birth weight (i.e., change in grams) and \( d \) to the prevalence difference of confounder \( U \) between levels of exposure. By subtracting each combination of \( g \times d \) from the \( \beta_1 \) coefficient and 95% confidence interval estimated by model 3, we located bounds within which our findings remained valid under the specified scenario. We set the ranges of values for \( g \) and \( d \) to be feasible values drawn from our SEM and consistent with the literature. For example, since prenatal smoking is a strong determinant of birth weight observed in the literature (28, 30), the upper limits for \( g \) were set at a level close to the effect of prenatal smoking observed in our SEM. Similarly, we set the upper limit of \( d \) to be ±25%, which was close to the difference in prenatal smoking prevalence between high and low \( G_1 \) adult SES estimated in our SEM.

All data processing and analysis were conducted in Stata 12.1 MP.

RESULTS

Overall, 21%, 63%, and 16% of G0s in the analytical population reported educational levels of less than high school, high school diploma or equivalent, and college degree at the time of \( G_1 \)’s birth, respectively. Mean \( G_2 \) birth weight was 3,220 g, 3,268 g, and 3,309 g among G0s with less than high school, a high school diploma or equivalent, and a college degree, respectively (Table 1).

Adjusting for prepregnancy overweight and other covariates through multivariable regression (model 1), we estimated 45-g (95% confidence interval (CI): −28.0, 118.8) and 54-g (95% CI: −14.0, 122.1; Table 2) higher \( G_2 \) birth weights for each increase in \( G_0 \) educational level in models controlling for continuous and dichotomized mediators, respectively. Leaving prepregnancy overweight out of the model (model 2)

### Table 2. Multivariable Linear Regression Estimates of the Association of \( G_0 \) Education With \( G_2 \) Birth Weight (*n* = 1,681), With and Without Adjustment for Prepregnancy Overweight, National Longitudinal Study of Adolescent to Adult Health, United States, 1995–2009

<table>
<thead>
<tr>
<th>Model</th>
<th>Adjusted for Prepregnancy Overweight*</th>
<th>Not Adjusted for Prepregnancy Overweight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for Prepregnancy Overweight*</td>
<td>Not Adjusted for Prepregnancy Overweight</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td>No factor scoresb</td>
<td>45.4</td>
<td>−28.0, 118.8</td>
</tr>
<tr>
<td>Childhood maltreatment factor score onlyc</td>
<td>47.2</td>
<td>−25.9, 120.2</td>
</tr>
<tr>
<td>Adult SES factor score onlyd</td>
<td>45.6</td>
<td>−26.5, 117.6</td>
</tr>
<tr>
<td>Both factor scorese</td>
<td>47.5</td>
<td>−24.0, 119.1</td>
</tr>
<tr>
<td>Dichotomized mediatorsf</td>
<td>54.1</td>
<td>−14.0, 122.1</td>
</tr>
<tr>
<td>Multiple imputationg</td>
<td>47.7</td>
<td>−16.5, 111.9</td>
</tr>
</tbody>
</table>

**Table 3. Marginal Structural Model Estimates of Determinants of \( G_2 \) Birth Weight (*n* = 1,681), National Longitudinal Study of Adolescent to Adult Health, United States, 1995–2009**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>β</th>
<th>95% CI</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0 education</td>
<td>86.7</td>
<td>10.9, 162.5</td>
<td>0.025</td>
</tr>
<tr>
<td>High G1 childhood maltreatment</td>
<td>−41.6</td>
<td>−126.1, 42.9</td>
<td>0.332</td>
</tr>
<tr>
<td>Low G1 adult SES</td>
<td>−117.7</td>
<td>−205.0, −30.4</td>
<td>0.009</td>
</tr>
<tr>
<td>Any G1 prenatal smoking</td>
<td>−122.0</td>
<td>−234.6, −9.5</td>
<td>0.034</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; G0, generation 0 (grandmother); G1, generation 1 (mother/respondent); G2, generation 2 (grandchild); SES, socioeconomic status.
produced slightly smaller estimates of association, between 33 g and 45 g per G0 educational category, suggestive of residual confounding. Estimates from the dichotomous mediator model after multiple imputation produced estimates of 47.7 g and 57.3 g for adjusted and unadjusted models, respectively (Table 2). Our SEM provided supportive evidence for the confounding influence of G0 race and age at G1 birth, with 2 exceptions: We found no association between G0 non-white status and G1 childhood maltreatment, and we found an unexpected positive association between G1 high maternal education and high adult SES (Figure 2).

Using an MSM estimated by inverse probability weighting, we found an 87-g higher (95% CI: 10.9, 162.5) G2 birth weight for each increase in G0 educational level, controlled for life-course mediators (Table 3). Associations between G2 birth weight and other mediators were in expected directions, with proximal determinants such as G1 prenatal smoking having the strongest magnitude of association. We found weaker evidence for a controlled direct effect of G0 education on G2 birth weight upon incorporating preterm birth as a mediator (β = 65.1, 95% CI: −1.4, 131.5; Table 4). Other sensitivity analyses did not alter interpretations greatly (Table 4). Notably, truncating weights to limit the influence of outlying exposure types only strengthened associations, albeit at the cost of exposure model misspecification (37). Moreover, data replacement techniques did not greatly alter the magnitude or precision of estimates, though confidence intervals were generally wide. Under the hypothetical bias scenarios, we found that a single binary confounder would have to differ in prevalence between exposure groups by at least 25% (and affect G2 birth weight by approximately 50 g) or have an effect on G2 birth weight of 150 g (and differ by approximately 10%) to fully explain our findings (Table 5).

**DISCUSSION**

Overall, we found fairly robust evidence for an association between grandmaternal (G0) education at the time of a mother’s (G1) birth on the birth weight of her grandchild (G2), independent of the mother’s mediating life course. We found an 87-g (95% CI: 10.9, 162.5) higher G2 birth weight associated with each increase in G0 educational level (less than high school, high school diploma or equivalent, or college degree), after adjusting for childhood maltreatment, low adult SES, prenatal smoking, and endogenous confounding by pre-pregnancy BMI. Our findings were robust to tested model alterations, data replacement, and several unmeasured confounding scenarios.

Early-life determinants of pregnancy outcomes are of particular interest (2), particularly because of the insensitivity of low birth weight to known interventions (42). There is some biological plausibility for an association between lower grandmaternal educational status and grandchild birth weight through glucocorticoid exposure and hypothalamic-pituitary-adrenal axis programming pathways (5–9). However, prior empirical studies on associations between grandparental education and grandchild birth have not provided consistent evidence (9, 10): In a study of predominantly African Americans and low-income whites, Astone et al. (9) found high grandmaternal education to be associated with a 181-g increased grandchild birth weight among mothers with a high school education or less. However, Kwock et al. (10) found no such association after adjusting for parental education. The potential influence of endogenous confounding was not tested in either study. Controlling for endogenous confounding by maternal prepregnancy BMI, a strong determinant of birth weight, we found relatively strong evidence for an association.
Table 5. Results From Quantitative Bias Analysis of the Effect of an Unmeasured Binary Confounder on the Estimated Controlled Direct Effect of G0 Education on G2 Birth Weight, National Longitudinal Study of Adolescent to Adult Health, United States, 1995–2009a

<table>
<thead>
<tr>
<th>d, %</th>
<th>-150 g Adjusted β</th>
<th>95% CI</th>
<th>-100 g Adjusted β</th>
<th>95% CI</th>
<th>-50 g Adjusted β</th>
<th>95% CI</th>
<th>50 g Adjusted β</th>
<th>95% CI</th>
<th>100 g Adjusted β</th>
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<tr>
<td>-25</td>
<td>49.2b</td>
<td>-26.6, 125.0</td>
<td>61.7b</td>
<td>-14.1, 137.5</td>
<td>74.2b</td>
<td>-1.6, 150.0</td>
<td>99.2</td>
<td>23.4, 175.0</td>
<td>111.7</td>
<td>35.9, 187.5</td>
<td>124.2</td>
<td>48.4, 200.0</td>
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<td>76.7</td>
<td>0.9, 152.5</td>
<td>96.7</td>
<td>20.9, 172.5</td>
<td>106.7</td>
<td>30.9, 182.5</td>
<td>116.7</td>
<td>40.9, 192.5</td>
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<tr>
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<td>71.7b</td>
<td>-4.1, 147.5</td>
<td>79.2</td>
<td>3.4, 155.0</td>
<td>94.2</td>
<td>18.4, 170.0</td>
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<td>89.2</td>
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Abbreviations: CI, confidence interval; G0, generation 0 (grandmother); G1, generation 1 (mother/respondent); G2, generation 2 (grandchild).

a For this analysis, point estimates (β) and 95% CIs were adjusted for a hypothetical, unmeasured binary confounder by subtracting a product of 2 bias parameters: d, indicating the imbalance of the confounder between strata of the exposure or mediator, and g, indicating the effect of the confounder on the outcome.

b These adjusted estimates have 95% CIs that encompass zero; therefore, a confounder with the corresponding bias parameters would be sufficient to explain the original controlled direct effect estimate. That is, the first column demonstrates that an unmeasured binary confounder associated with a 150-g lower G2 birth weight would have to be 5%–10% less prevalent among highly educated grandmothers to account for the original estimate. For comparison, any G1 prenatal smoking was 6.4% lower among college-educated grandmothers than among grandmothers with less than a high school education and was associated with a 118-g reduction in G2 birth weight.
Our approach contributed several strengths to this investigation. First, prominent determinants of birth weight, including prepregnancy BMI, prenatal smoking, and self-reported race (28) and mediation by childhood maltreatment (25), were explicitly included in our models. Second, we addressed the possibility of incorrect model specification and mismeasurement through a variety of techniques and found that these scenarios had little influence on estimates. For example, it is plausible that adult SES influences prepregnancy BMI. Neither swapping the causal ordering (through reweighting) nor using alternative (i.e., earlier wave) measures of these mediators appeared to greatly affect estimates. Additionally, the consistent estimates across models that adjusted for different covariate parameterizations (Table 2) suggest that residual confounding from dichotomization was not likely to be responsible for our MSM findings. Dichotomization at other cutoffs for low adult SES or childhood maltreatment did not change our substantive interpretations. In fact, using the 20th percentile as the cutpoint for low adult SES strengthened estimated associations (results not shown). Our quantitative bias analysis suggested that a single binary confounder would need to be fairly strong and imbalanced across exposure groups to fully explain our estimates. Third, confidence in our findings is also improved by the concurrence of secondary model findings with past literature: Notably, we observed greater strengths of association between G2 birth weight and proximate G1 mediators, prenatal smoking and adult SES, than between G2 birth weight and childhood maltreatment using the MSM. In addition, the magnitude of birth weight reduction due to prenatal smoking was in line with findings from past meta-analyses (28, 43). Finally, our choice to estimate a controlled direct effect allowed us to address the question, What association with grandmaternal education remains even after strictly controlling more proximal, life-course determinants of birth weight outcome? Finding an association in this context helps provide justification for continued investigation of early-life factors despite the prevailing clinical focus on modifiable perinatal maternal factors. Furthermore, unlike the case with natural direct effect estimation, we were able to avoid cross-world assumptions (44).

Some limitations of our study are worth highlighting. In spite of several sensitivity and bias analyses, model misspecification and unmeasured confounding were still possible. In recent publications, several authors have questioned the ability of conventional observation methods to completely account for these issues (45, 46). We attempted to address these limitations through model alterations (Web Tables 5–13) and by quantifying the influence of potential unmeasured confounders. However, it is still possible that several nonbinary unmeasured confounders may collectively explain our findings (22, 41). Since Add Health was not designed to investigate characteristics surrounding the respondent’s (G1) birth, we were limited in our ability to incorporate potentially interesting G1 perinatal exposures. These include infection, air pollution, G0 nutrition, and smoking. When breastfeeding duration and G0 smoking during G1 adolescence (Web Table 5) were incorporated into our MSM analyses, point estimates and confidence intervals were virtually unchanged. Since our study relied almost solely on self-reports (with the exception of wave III BMI), bias due to measurement error is also a concern. Specifically, recall of childhood maltreatment and prenatal smoking may be differentially misclassified by grandmaternal and maternal SES. Notably, this may explain the unexpected positive association between childhood maltreatment and adult SES in our SEM.

Finally, we stress that findings from our study should be interpreted as suggestive associations rather than estimates of causal effects per se. Education represents a state which may be achieved through a variety of pathways and consequently (47) may be indicative of 1 or more true causal exposures with varying influences on early-life environment and future pregnancy outcome. Nonetheless, the identification of a consistent, direct association between an early-life factor and pregnancy outcome under various causal assumptions coupled with a variety of sensitivity approaches supports the pursuit of more specific early-life causal exposures that may explain the role of education as a fundamental, transgenerational determinant of health (48). Further research on biological mechanisms—for example, fetal glucocorticoid exposure due to maternal education-related stressors (5–7)—may help to identify more precise causal effects.

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Conflict of interest: none declared.

REFERENCES