Fetal growth and psychiatric and socioeconomic problems: population-based sibling comparison

Quetzal A. Class, Martin E. Rickert, Henrik Larsson, Paul Lichtenstein and Brian M. D’Onofrio

Background
It is unclear whether associations between fetal growth and psychiatric and socioeconomic problems are consistent with causal mechanisms.

Aims
To estimate the extent to which associations are a result of unmeasured confounding factors using a sibling-comparison approach.

Method
We predicted outcomes from continuously measured birth weight in a Swedish population cohort (n = 3,291,773), while controlling for measured and unmeasured confounding.

Results
In the population, lower birth weight (<2500 g) increased the risk of all outcomes. Sibling-comparison models indicated that lower birth weight independently predicted increased risk for autism spectrum disorder (hazard ratio for low birth weight = 2.44, 95% CI 1.99–2.97) and attention-deficit hyperactivity disorder. Although attenuated, associations remained for psychotic or bipolar disorder and educational problems. Associations with suicide attempt, substance use problems and social welfare receipt, however, were fully attenuated in sibling comparisons.

Conclusions
Results suggest that fetal growth, and factors that influence it, contribute to psychiatric and socioeconomic problems.

Declaration of interest
None.

Sample
After approval from the Institutional Review Boards at Karolinska Institutet and Indiana University, we created a prospective national cohort by linking information in the following Swedish registries: (a) the Medical Birth Register includes data on more than 99% of all pregnancies in Sweden; (b) the Multi-Generation Register contains information about the biological relationships of all in-patient hospital admissions since 1973 and out-patient care since 2001; (f) the National Crime Register includes information about all criminal convictions; (g) the National School Register includes all subject grades at the end of grade 9 since 1983; (h) the Education Register contains information on the highest level of completed formal education; and (i) the longitudinal integration database for health insurance and social studies (LISA) contains yearly assessments of childbearing, marital and social welfare status for all individuals at least 15 years old since 1990. Detailed information about these registers is available in the online data supplement and elsewhere.

The data-set began with 3,619,712 offspring born from 1973 to 2008. We removed multiple births (86,273, 2.4%) because birth outcomes are different in multiples as compared with singleton births. We also removed offspring with missing birth weight designs and examined the effect sizes using sibling-comparison models. Quasi-experimental approaches, such as sibling-comparison approaches, utilise design features to test alternative explanations. By accounting for genetic and environmental factors that make siblings similar, sibling comparisons offer a way to pull apart genetic and environmental confounding. Sensitivity analyses were used to test alternative explanations and address limitations inherent in the sibling-comparison approach.
information (9888, 0.3%) as well as recorded gestational age values of less than 23 weeks or greater than 42 weeks and 6 days (49 374, 1.4%). Offspring with no information regarding gender (3, <0.1%), invalid parity information (20, <0.1%) and those who had emigrated within the 25 year period (182 223, 5.0%) were removed. We also excluded offspring missing maternal identification numbers (158, <0.1%). The final sample consisted of 3 291 773 offspring born to 1 735 250 distinct biological mothers, representing 90.9% of all recorded Swedish births within the year range investigated.

Both ASD and ADHD were identified using in-patient and out-patient assessment information24 from individuals born between 1980 and 2001 (n = 2 032 803). In addition, we used a 2-year age criterion for ASD and ADHD diagnosis. For criminality, we used an age criterion of 15 years because of the Swedish legal age of responsibility. Therefore, the criminality subsample spanned the years 1973–1994 and included 2 044 992 individuals. For all other outcomes, we used a 12 year age criterion. Therefore, this subsample included 2 308 032 offspring born between 1973 and 1997.

**Measures**

**Birth weight**

To assess fetal growth, we utilised two different representations of birth weight while controlling for gestational age at birth. For the ordinal representation, birth weight was grouped into the following ranges: <2500 g, 2501–3000 g, 3001–3500 g, 3501–4000 g (referent) and >4000 g. Continuously measured birth weight was converted to a linear scale centred at 3750 g (reference 0 point), the approximate mean of the sample.

**Offspring outcomes**

We predicted six indices of psychiatric problems previously shown to be reliable measures.29–32 In particular (a) ASD and (b) ADHD were indexed using validated29,33 in-patient and out-patient diagnoses according to ICD-934 and ICD-1035 for offspring born between 1980 and 2001 and being at least 2 years old at the time of diagnosis. As the ICD follows a strict definition of ADHD and ASD, results apply to the most severe cases of these disorders. In addition, it was not possible to classify ADHD according to subtype (i.e. combined, primarily hyperactive–impulsive and primarily inattentive type), since these were not recorded across the registers using the ICD. Offspring had to have been at least 12 years old to receive any of the following disorders: (c) psychotic or bipolar disorder was defined as first in-patient admission for schizophrenia, bipolar disorder or another non-organic psychotic disorder according to ICD-8,9 -9 and -10 criteria;25 (d) substance use problems was defined as first in-patient admission for a primary or secondary diagnosis of alcohol or any other non-nicotine substance use disorder;30 (e) age at suicide attempt was gathered using in-patient admission for a primary or secondary diagnosis;31 and (f) criminality was indicated by the first occurrence of any criminal conviction from age 15 years, the age of legal responsibility in Sweden.32 We chose not to examine broadly defined affective disorder because in-patient admissions for that diagnosis may indicate the presence of co-occurring suicidality or psychosis, and we had access to validated indicators of these associated possible outcomes.9,31 Respective ICD codes are presented in online Table DS1, and it should be noted that clinical evaluations, not structured interviews, were used by diagnosing medical providers to determine primary diagnoses.

We predicted three indices of socioeconomic outcomes: (a) failing grades indexed poor school performance in grade 9 commensurate with a mean failing grade across 16 academic subjects;37 (b) education under 10 years was an indication of low educational attainment38 and (c) social welfare receipt, which was defined as the age of first receipt of government social welfare subsidies. For verification and converging support of these outcomes, we also predicted low income and higher education (further explained in online Fig. DS2).

**Covariates**

The Medical Birth Register provided offspring gender, birth order, year of birth and gestational age at birth. Measured maternal and paternal covariates included age at the offspring’s birth, highest level of completed education by 2008 (to capture some socioeconomic variability across families) and lifetime history of any criminal conviction. All covariates were associated with both birth weight and the outcomes.

**Analyses**

We used Cox survival analysis for right-censored outcomes because not all offspring have lived through the study period. If offspring did not receive a diagnosis within the study period, they contributed person-time at risk until death, emigration or the end date of follow-up (31 December 2009), whichever came first. We used logistic regression analyses when predicting failing grades and education under 10 years because they were dichotomous outcomes. Thus, results are presented as hazard ratios (HRs) or odds ratios (ORs).

We fit a series of models for each outcome. All models controlled for offspring gender, birth order and measures of linear and quadratic gestational age. Logistic models also controlled for offspring year of birth. Because we always adjusted gestational age at birth, our predictor may be considered an index of fetal growth. The first statistical model used the ordinal representation of birth weight to estimate clinically interpretable estimates of risk across outcomes. Second, we used a continuous representation of birth weight in two baseline models. One baseline model included both a linear and quadratic representation of birth weight, whereas the other baseline model only included the linear representation of birth weight. Akaiake information criterion, a measure of relative merit that penalises for model complexity, was used to select the best fitting model, either linear or quadratic. Third, we included offspring-specific (gender, birth order, linear and quadratic gestational age and maternal and paternal age at childbirth) and parental-specific covariates (maternal and paternal highest level of education and history of criminal conviction) in an adjusted model of either continuous linear or quadratic representation of birth weight. Fourth, we fitted a fixed-effects model that clustered at the maternal level, which accounted for factors that siblings share, including all genetic and environmental factors that make siblings similar.24 Covariates that may vary between siblings (i.e. offspring gender, birth order, gestational age and offspring year of birth in logistic models) were included in fixed-effects models. Siblings were identified as individuals sharing a biological mother (for example full or maternal half-siblings).

**Sensitivity analyses**

We ran several sensitivity analyses to test for biases because of preterm births, to examine whether there was converging evidence across related socioeconomic outcomes and to check assumptions inherent in the sibling-comparison design.

**Results**

Table 1 presents cohort demographics by birth weight category. Table 2 presents the number of offspring across outcomes by birth weight category.
Table 1 Demographic characteristics of 3,291,773 offspring born 1973–2008 in Sweden by birth weight

<table>
<thead>
<tr>
<th>Covariates</th>
<th>≤ 2500 (n = 114,580)</th>
<th>2501–3000 (n = 366,500)</th>
<th>3001–3500 (n = 1,075,447)</th>
<th>3501–4000 (n = 1,152,337)</th>
<th>≥ 4000 (n = 583,909)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offspring, birth year: 1973–2008 (n = 3,291,773)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>58,657 (51.19)</td>
<td>207,481 (56.61)</td>
<td>573,332 (53.31)</td>
<td>532,202 (46.27)</td>
<td>220,119 (37.70)</td>
</tr>
<tr>
<td>Gestational age, mean (s.d.)</td>
<td>245.66 (25.33)</td>
<td>271.19 (12.10)</td>
<td>278.14 (9.41)</td>
<td>282.14 (8.27)</td>
<td>285.24 (7.77)</td>
</tr>
<tr>
<td>Maternal, birth year: 1924–1995 (n = 1,732,107)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at birth, mean (s.d.)</td>
<td>31.75 (6.55)</td>
<td>31.38 (6.28)</td>
<td>31.49 (6.07)</td>
<td>31.78 (5.96)</td>
<td>32.28 (5.91)</td>
</tr>
<tr>
<td>Nationality, Swedish: n (%)</td>
<td>52,049 (83.61)</td>
<td>165,781 (82.69)</td>
<td>485,000 (84.50)</td>
<td>518,434 (87.04)</td>
<td>259,048 (89.02)</td>
</tr>
<tr>
<td>Upper secondary education: n (%)</td>
<td>27,192 (43.63)</td>
<td>90,199 (44.92)</td>
<td>274,812 (47.82)</td>
<td>294,778 (49.44)</td>
<td>145,192 (49.84)</td>
</tr>
<tr>
<td>Adult severe psychopathology: n (%)</td>
<td>1,345 (2.16)</td>
<td>4,033 (2.01)</td>
<td>10,059 (1.75)</td>
<td>9,399 (1.58)</td>
<td>4,772 (1.43)</td>
</tr>
<tr>
<td>Maternal, birth year: 1904–1993 (n = 1,725,359)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at birth, mean (s.d.)</td>
<td>31.75 (6.55)</td>
<td>31.38 (6.28)</td>
<td>31.49 (6.07)</td>
<td>31.78 (5.96)</td>
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</tr>
</tbody>
</table>
| Psychiatric problems

Figure 1 presents results from the baseline ordinal model (dark bars) with 95% confidence intervals. The corresponding results using the continuous measure of birth weight (the solid line in Fig. 1) also illustrate how fetal growth was associated with later psychiatric problems. For ease of interpretation, ordinal results are discussed here and continuous results are presented graphically.

Figure 1(a)–(c) present the strong inverse association between birth weight and ASD (HRBW: ≤ 2500 g = 1.79, 95% CI 1.64–1.96), ADHD (HRBW: ≤ 2500 g = 1.54, 95% CI 1.44–1.65), and psychotic or bipolar disorder (HRBW: ≤ 2500 g = 1.19, 95% CI 1.09–1.29) respectively. The associations remained robust when adjusting for offspring- and parental-specific covariates (not shown; see online Table DS2). Also in Fig. 1, the findings from fixed-effects modelling, which compared differentially exposed siblings (light bars with 95% confidence intervals and the dotted line), showed consistently elevated effect sizes for these outcomes. Fetal growth was associated with ASD (HRBW: ≤ 2500 g = 2.44, 95% CI 1.99–2.97), ADHD (HRBW: ≤ 2500 g = 1.65, 95% CI 1.40–1.93) and psychotic or bipolar disorder (HRBW: ≤ 2500 g = 1.24, 95% CI 1.02–1.51) independent of the measured covariates and the comparison of differentially exposed siblings, consistent with a causal inference.

A different pattern of results was found when predicting suicide attempt and substance use problems (Fig. 1(d) and (e)), however. As can be noted in the dark bars in Fig. 1, population models suggested that lower birth weight increased the risk for suicide attempt (HRBW: ≤ 2500 g = 1.19, 95% CI 1.11–1.28) and substance use problems (HRBW: ≤ 2500 g = 1.27, 95% CI 1.20–1.34). After adjusting for measured covariates (not shown; see online Table DS2) and in fixed-effects models (Fig. 1, light bars), the associations with suicide attempt (HRBW: ≤ 2500 g = 1.94, 95% CI 0.81–1.10) and substance use problems (HRBW: ≤ 2500 g = 0.93, 95% CI 0.83–1.04) were fully attenuated.

The pattern of association was distinct when predicting criminality (Fig. 1(f)). More specifically, while population models showed that lower birth weight increased the risk for criminality...
(HRBW < 2500 g = 1.15, 95% CI 1.12–1.18), the direction of association switched in fixed-effects models. In the fixed-effects models, lower birth weight was slightly protective against criminality (HRBW < 2500 g = 0.87, 95% CI 0.83–0.92).

As can be seen in Fig. 1, all psychiatric outcomes except suicide attempt and substance use problems were better explained by a quadratic representation of birth weight (see online Table DS4 for Akaike information criterion for linear and quadratic models). Adjusted models are not presented here or in Fig. 1 for ease of interpretation. Parameter estimates across all ordinal bins are presented in online Table DS4.

**Socioeconomic outcomes**

Figure 2 (a)–(c) present findings across ordinal and continuous birth weight representation for failing grades, education under 10 years and social welfare receipt, respectively. Population estimates suggested that lower birth weight was associated with increased risk for failing grades (HRBW < 2500 g = 1.66, 95% CI 1.62–1.71) and education under 10 years (HRBW < 2500 g = 1.46, 95% CI 1.42–1.49). These are presented in Fig. 2 with dark bars (ordinal) and a solid line (continuous). Fixed-effects models showed attenuated, although consistent, results for failing grades (HRBW < 2500 g = 1.07, 95% CI 1.01–1.13) and education under 10 years (HRBW < 2500 g = 1.18, 95% CI 1.12–1.24), as seen in the light bars (ordinal) and dotted line (continuous) in the figure. Thus, the results lend support to fetal growth being in the causal path towards failing grades and education under 10 years. A different pattern emerged for social welfare receipt, however (Fig. 2(c)). Although the population estimate for social welfare receipt showed that lower birth weights are associated with increased social welfare receipt (HRBW < 2500 g = 1.52, 95% CI 1.49–1.55), the relation was completely attenuated in the fixed-effects model (HRBW < 2500 g = 1.00, 95% CI 0.95–1.05).

**Sensitivity analyses**

First, to test whether results were biased by premature births, we limited the sample to full-term births only. Online Fig. DS1 shows that associations are comparable with those found in the main analyses, thus premature births were not driving the associations found. Second, we predicted two additional outcomes related to our main socioeconomic outcomes, low income and higher education. From these analyses we obtained converging evidence about the robust association between fetal growth and decreased odds of educational attainment, as well as the fully attenuated relationship between fetal growth and economic stability (online Fig. DS2). Third, we performed analyses to address some of the assumptions of the sibling-comparison design. To address concerns about the generalisability of findings from offspring to siblings to those without, we compared the population estimates in families with multiple children to those with only one child. Online Fig. DS3 shows that baseline population estimates were not different between offspring with one or more siblings as compared with only children. To address concerns about the generalisability of the findings from differentially exposed sibling to other populations, we conducted cousin-comparisons. Online Fig. DS4 presents the cousin-comparison results showing a commensurate...
The current study examined the degree to which familial confounding, because of genetic and shared environmental factors, accounts for the associations between fetal growth, indicated by birth weight while controlling for gestational age, and psychiatric and socioeconomic problems. We used a large, well-validated, population-based data-set. The size and scope of the data-set provided us with the opportunity to examine rare and serious outcomes while studying the specificity of our findings across a broad range of outcomes. Further, the data structure allowed us to utilise quasi-experimental designs (for example sibling- and cousin-comparison) with precise measures of predictors and covariates. This is one of the first studies on fetal sibling- and cousin-comparison analyses provided evidence against alternative explanations for the findings. Despite some attenuation in fixed-effects models, the results support to the conclusion that fetal growth is along a causal pathway for these outcomes. Our findings also complement previous sibling-comparison research focusing on the long-term outcomes following early gestational age at birth.26

Across outcomes, and in agreement with most previous research,2–8,26,39 the population estimates suggested that impaired fetal growth, as evidenced by lower birth weights, was associated with greater risk of each outcome. Results from sibling-comparison analyses showed that associations are consistent with causal inferences in an outcome-dependent manner. After fitting sibling-comparison fixed-effects models, the results support causal inferences between fetal growth and ASD, as well as ADHD. Despite some attenuation in fixed-effects models, the relation between fetal growth and psychotic or bipolar disorder, as well as failing grades and education less than 10 years, also supports a causal inference. Therefore, genetic and/or environmental factors specific to fetal development, as indexed by lower birth weight, influence the likelihood of these outcomes. In contrast, our results showed attenuation of the associations between fetal growth and suicide attempt, substance use problems and social welfare receipt, thus suggesting that these associations are primarily as a result of selection effects correlated with fetal growth. Additionally, sensitivity analyses provided evidence against alternative explanations for the findings.

Discussion

The associations between birth weight and ADHD and ASD were independent of shared familial confounds and statistical covariates, as the magnitudes of association remained significantly elevated in fixed-effects models. Although some previous research has reported null findings,1,5,11 the current results build on previous co-twin control24–32 and epidemiological study findings.3 The associations between birth weight and psychotic or bipolar disorder were also independent of shared familial confounds and statistical covariates, although the magnitudes of association were attenuated in fixed-effects models. Even more attenuated, although still present, were the associations between birth weight and educational attainment variables in the fixed-effects models.5–8,39 The interpretation of sensitivity analyses that examined the associations in full-term births only, in families with only one child and when comparing differentially exposed cousins (see online Fig. DS1, DS3, and DS4, respectively) did not differ from the main results. Therefore, overall, our findings lend greater support to the conclusion that fetal growth is along a causal pathway for these outcomes. Our findings also complement previous sibling-comparison research focusing on the long-term outcomes following early gestational age at birth.26

Comparing the associations across these outcomes, fetal growth appears to be more strongly related to early-onset neurodevelopmental disorders such as ADHD and ASD than for distal markers of neurodevelopmental problems, such as educational problems and later-onset disorders, such as psychotic or bipolar disorder. As evidence across studies converge on a consistent picture of the role of fetal growth on these outcomes, future research must examine possible mediating mechanisms. For example, previous research has shown white matter abnormalities because of brain injury associated with low birth weight.40 Other differences in brain development that correspond with neurodevelopmental problems, such as the amount of cortical surface area, brain volume and caudate volume, have also been noted even across variations within normal birth weight.41 Poor in utero nutrition may also be contributing to different fetal growth and altered brain development.42 ADHD and ASD have been shown to share common genetic aetiology,43 which will also have to be explored.

We also found that impaired fetal growth was associated with a decreased likelihood of criminality after fixed-effects modelling...
and across the sensitivity analyses. This result supports previous fetal growth and gestational age research.\textsuperscript{26,44} Fetal-growth-impaired individuals may display personality characteristics linked with decreased risk-taking behaviours, receive increased parental monitoring and/or form fewer relationships with delinquent peers. Investigating violent v. non-violent crimes may elucidate the association further.\textsuperscript{45}

**Associations fully attenuated**

Once the genetic and environmental factors that siblings were controlled, the associations between fetal growth and substance use problems, suicide attempt and social welfare receipt were fully attenuated.

We also found converging evidence for social welfare receipt when predicting low income (see online Fig. DS2). The lack of association with substance use problems is in contrast to a previous co-twin control\textsuperscript{21} and an epidemiological\textsuperscript{5} study showing heavier infants were at increased risk for alcohol and drug use than lower birth weight infants, although measurement varies across studies.

**Strengths and limitations**

The sibling-comparison design allowed us to begin to address possible genetic confounding\textsuperscript{46} while also offering improved generalisability from a co-twin control approach. Fetal growth differences in twins may be aetiollogically distinct from fetal growth differences between singletons, and twins have a greater risk for growth restriction \textit{in utero} than singletons.\textsuperscript{57} Through the sensitivity analyses, we also explicitly tested some assumptions of the sibling-comparison design.\textsuperscript{47} Other sensitivity analyses included examining whether associations were driven by gestational age extremes, searching for converging evidence across related outcomes, and using continuously measured birth weight. Further, it should be noted that although our predictor was birth weight, we adjusted all associations for gestational age at birth. Therefore, we consider the predictor an index of fetal growth.

Despite these strengths, however, several limitations must be considered and addressed in future research. Sibling comparisons are not randomised controlled studies; therefore, the design cannot rule out all possible confounding factors and causation cannot be proven. Independent risk associated with fetal growth factors have been shown by comparing birth-weight-discordant monozygotic twins,\textsuperscript{3} which suggest such genetic factors do not explain the associations. Fixed-effects models also have lower statistical power than population-based estimates.\textsuperscript{47} Additional quasi-experimental research that relies on methods with different assumptions and limitations than the sibling-comparison approach is warranted.\textsuperscript{23} Replication in other countries, especially in countries differing in healthcare availability, is also needed.

**Implications**

Our findings contribute to the aetiological theory of neuro-developmental disorders and socioeconomic outcomes, as causal inferences were divided by outcome type. The results suggest that efforts be made to reduce the incidence of low-birth-weight births. Results also call for public health initiatives providing services that target risks co-occurring with impaired fetal growth, as the associations between birth weight and substance use problems, suicide attempt, and social welfare receipt were as a result of selection factors that co-occur with birth weight. Further, our findings open an interesting line for future researchers to explore what factors associated with impaired fetal growth contribute to the decreased risk of criminality we identified in sibling-comparison analyses. Overall, the current study emphasises the importance of continued research on the role of fetal growth factors in offspring psychiatric and socioeconomic problems.

**References**


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Description of Swedish population-based registers with references and participant flow

The data were obtained by linking information available in the following government-maintained, Swedish population-based registries: (1) the Medical Birth Registry includes data on more than 99% of pregnancies in Sweden since 1973 [1, 2]; (2) the Multi-Generation Register [3] contains information about biological and adoptive relationships living in Sweden since 1933; (3) the Migration Register contains dates for migration into or out of Sweden; (4) the Cause of Death Register contains dates and causes of all deaths since 1958; (5) the National Patient Registry [4] provides data on all psychiatric inpatient admissions in Sweden since 1973 and outpatient care since 2001. Every record includes the discharge date, primary discharge diagnosis, and up to seven secondary diagnoses assigned by the treating medical doctor using WHO’s ICD-10 codes since 1997 [5]; (6) the National Crime Register includes detailed information about all criminal convictions in lower court since 1973 on those aged 15 (the age of criminal responsibility) and older [6]; (7) the National School Register [7] includes grades across subjects for students at the end of grade nine (approximately age 16 years) since 1983; (8) the Education Register contains information on highest level of completed formal education between 1988 and 2008; (9) the longitudinal integrated database for health insurance and social studies (LISA) [8] contains yearly assessments of income, marital status, unemployment status, social welfare status, and education for all individuals 16 years of age and older since 1990.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Data Source</th>
<th>ICD Version</th>
<th>ICD Codes</th>
<th>Description</th>
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<tr>
<td><strong>Psychiatric Problems</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>ADHD</td>
<td>PR</td>
<td>9,10</td>
<td>314, F90</td>
<td>Hyperkinetic syndrome and attention-deficit hyperactivity disorders</td>
</tr>
<tr>
<td>ASD</td>
<td>PR</td>
<td>9, 10</td>
<td>299, F84</td>
<td>Includes disintegrative psychosis, Heller’s syndrome, and schizophrenic syndrome of childhood</td>
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<tr>
<td>Psychotic or Bipolar Disorder</td>
<td>PR</td>
<td>8, 9, 10</td>
<td>295, F20</td>
<td>Schizophrenia</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>296.1, 296.2, 296.9, 297-299, 296.X, F32.3 x.5 in F10-F19</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other non-organic psychoses</td>
</tr>
<tr>
<td>Suicide Attempt</td>
<td>PR</td>
<td>8, 9, 10</td>
<td>E950-E959, E980, X60-X84, Y70, Y10-Y34, Y872</td>
<td>Certain and uncertain attempts including violent, non-violent, other</td>
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<tr>
<td>Substance Use Problem</td>
<td>PR</td>
<td>8, 9, 10</td>
<td>303, 304, 305A, 305X, F10 (except x.5), F11-F19 (except x.5)</td>
<td>Alcohol and drug abuse (excludes nicotine)</td>
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<tr>
<td>Criminality</td>
<td>NCR</td>
<td>NA</td>
<td>NA</td>
<td>Earliest conviction date for any criminal act</td>
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<td><strong>Socioeconomic Outcomes</strong></td>
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<td>Failing Grades</td>
<td>NSR</td>
<td>NA</td>
<td>NA</td>
<td>Poor school performance across all 16 academic subjects in grade 9 (about age 16)</td>
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<tr>
<td>Education under 10 years</td>
<td>ER</td>
<td>NA</td>
<td>NA</td>
<td>Low educational attainment</td>
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<td>NA</td>
<td>Three or more years of postsecondary education</td>
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<tr>
<td>Social Welfare Benefits</td>
<td>LISA</td>
<td>NA</td>
<td>NA</td>
<td>Age at first receipt of government social welfare subsidies</td>
</tr>
</tbody>
</table>

Note: ASD = Autism spectrum disorder; PR = Patient Register; NCR = National Crime Register; NSR = National School Register; ER = Education register; MBR = Medical Birth Register
### Table DS2 Unstandardised linear and quadratic regression coefficients for the baseline, adjusted, and fixed effects models.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Baseline Model</th>
<th></th>
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<td></td>
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<td>Linear term</td>
<td>Quadratic term</td>
<td>Linear term</td>
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<td>0.003</td>
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<td>-</td>
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<td>-0.003</td>
<td>0.003</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Note: ADHD=Attention Deficit Hyperactivity Disorder; ASD=Autism Spectrum Disorder; b=maximum likelihood estimate of the unstandardised regression coefficient; SE = estimated standard error; A dash(-) indicates that the p-value of the Wald chi-square test statistic for the quadratic parameter is greater than 0.05, and therefore not included in the model; bold coefficients have p-value < 0.05.
Table DS3 Comparison of Akaike information criterion fit indices across baseline linear and quadratic candidate models.

The model selection Table DS3 compares the Akaike information criterion (AIC) for the baseline model with linear (L) birth weight only and the baseline model with both linear and quadratic (L+Q) birth weight. The column labeled “AIC-min” indicates which of the two candidate models (L or L+Q) yielded the lowest AIC. The observed difference, \( \Delta \text{AIC} = \text{AIC}_L – \text{AIC}_{L+Q} \), provides a measure of relative merit that is free of scaling constants and can be interpreted as strength of evidence for model selection purposes [9].

Table DS3. Comparison of AIC values for linear and quadratic candidate models.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Candidate Model</th>
<th>Linear BW with Quadratic BW</th>
<th>AIC-min</th>
<th>( \Delta \text{AIC} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric Problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>844471.23</td>
<td>844370.62</td>
<td>L + Q</td>
<td>100.61</td>
</tr>
<tr>
<td>ASD</td>
<td>452237.10</td>
<td>452102.20</td>
<td>L + Q</td>
<td>134.90</td>
</tr>
<tr>
<td>Psychotic or Bipolar Disorder</td>
<td>539246.73</td>
<td>539235.29</td>
<td>L + Q</td>
<td>11.44</td>
</tr>
<tr>
<td>Suicide Attempt</td>
<td>863605.97</td>
<td>863607.04</td>
<td>L</td>
<td>-1.07</td>
</tr>
<tr>
<td>Substance Use Problem</td>
<td>1303851.20</td>
<td>1303852.90</td>
<td>L</td>
<td>-1.70</td>
</tr>
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<td>Criminality</td>
<td>7995423.10</td>
<td>7995413.10</td>
<td>L + Q</td>
<td>10.00</td>
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<tr>
<td>Socioeconomic Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failing Grades</td>
<td>1347757.50</td>
<td>1346626.00</td>
<td>L + Q</td>
<td>1131.50</td>
</tr>
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<td>Education under 10 yrs</td>
<td>1839981.20</td>
<td>1839871.00</td>
<td>L + Q</td>
<td>110.20</td>
</tr>
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<td>10651879.00</td>
<td>10651870.00</td>
<td>L + Q</td>
<td>9.00</td>
</tr>
</tbody>
</table>

Note: BW = birth weight; ADHD = Attention Deficit Hyperactivity Disorder; ASD = Autism Spectrum Disorder; L = model with linear birth weight only; L+Q = baseline model with both linear and quadratic birth weight.
Table DS4. Odds or Cox hazard regression parameter estimates for baseline and fixed effects models using ordinal birth weight.

Table DS4 presents the unstandardized regression coefficients with standard errors and the point estimates, either Odds Ratios or Hazard Ratios, with 95% confidence intervals associated with the ordinal bins of birth weight across baseline and fixed effects models. The baseline estimates presented here correspond with the point estimates presented in Fig. 1 within the main paper.

Estimates for fixed effects models using ordinal representation of birth weight provide a sensitivity analysis to examine the sibling comparison results absent of assumptions about the underlying pattern (i.e., linear or quadratic) of the associations between birth weight and the indices of mortality and morbidity. Figures 1 and 2 in the main paper provide a graphical comparison of the baseline and fixed effects models using ordinally represented birth weight. The fixed effects results using ordinal representation of birth weight give commensurate results with analyses based on linear and quadratic modeling presented in the main analyses. It can be noted, however, that the confidence intervals around fixed effects estimates using ordinal bins are larger than those presented in the main analyses due to the reduced statistical power in moving from a continuous representation of birth weight to ordinal bins. These results suggest that assumptions about the shape of model fitting using families with multiple offspring (which are the only informative families for the sibling comparison estimates) do not account for the fixed effects results using the continuous index of birth weight.

Table DS4 Odds or Cox hazard regression parameter estimates for baseline and fixed effects models using ordinal birth weight.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Model</th>
<th>BW bin (gm)</th>
<th>b</th>
<th>SE</th>
<th>ChiSq</th>
<th>Pr &gt; ChiSq</th>
<th>HR/OR</th>
<th>95%LCL</th>
<th>95%UCL</th>
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</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>Baseline</td>
<td>≤ 2500</td>
<td>0.433</td>
<td>0.03</td>
<td>159.864</td>
<td>&lt;.0001</td>
<td>1.542</td>
<td>1.442</td>
<td>1.649</td>
</tr>
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<td></td>
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<td>0.249</td>
<td>0.02</td>
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<td>1.232</td>
<td>1.335</td>
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<td>0.099</td>
<td>0.01</td>
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<td>&lt;.0001</td>
<td>1.104</td>
<td>1.072</td>
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<tr>
<td></td>
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<td>≥ 4001</td>
<td>0.059</td>
<td>0.02</td>
<td>11.599</td>
<td>0.001</td>
<td>1.061</td>
<td>1.025</td>
<td>1.097</td>
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<tr>
<td></td>
<td>Fixed effects</td>
<td>≤ 2500</td>
<td>0.498</td>
<td>0.08</td>
<td>37.288</td>
<td>&lt;.0001</td>
<td>1.646</td>
<td>1.403</td>
<td>1.932</td>
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<td>2501-3000</td>
<td>0.217</td>
<td>0.05</td>
<td>20.517</td>
<td>&lt;.0001</td>
<td>1.243</td>
<td>1.131</td>
<td>1.365</td>
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<td></td>
<td>3001-3500</td>
<td>0.120</td>
<td>0.03</td>
<td>14.237</td>
<td>0.000</td>
<td>1.127</td>
<td>1.059</td>
<td>1.199</td>
</tr>
<tr>
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<td>≥ 4001</td>
<td>-0.001</td>
<td>0.04</td>
<td>0.001</td>
<td>0.971</td>
<td>0.999</td>
<td>0.927</td>
<td>1.076</td>
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<tr>
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<td>0.04</td>
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<td>&lt;.0001</td>
<td>1.790</td>
<td>1.639</td>
<td>1.955</td>
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<td>1.206</td>
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<td>0.02</td>
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<td>1.015</td>
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<td>≥ 4001</td>
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</tr>
<tr>
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</tr>
<tr>
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<td>0.06</td>
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<th>Failing Grades Baseline</th>
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<th>2501-3000</th>
<th>3001-3500</th>
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<tr>
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<td>0.974</td>
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<td>1.041</td>
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<tr>
<td>Education under 10 yrs</td>
<td>Baseline</td>
<td>≤ 2500</td>
<td>0.376 0.01</td>
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<td>0.001</td>
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<td>------------------------</td>
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<td>--------</td>
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Note:  b = unstandardized regression coefficient; SE=standard error

BW = birthweight in grams

ADHD=Attention Deficit Hyperactivity Disorder;  ASD=Autism Spectrum Disorder
Figure DS1 Fixed effects parameter estimates when limiting sample to full term births only.

Compared with parameter estimates from the main analyses, which included all gestational ages, results from analyses limited to full term births did not substantially alter the results (Figure DS1). This suggests that associations presented in main analyses were not biased by extremely premature or late births. Figure DS1 presents main analyses figures as well as those limited to full term births only (right column). As can be seen in Figure DS1, when restricted to full term births only (right figure), parameters corresponding to the smallest ordinal category of birth weight were attenuated as compared with main analyses (left figure). Small sample size may also contribute to this attenuation.
Figure DS1 Comparison of birth weight predicting psychiatric and socioeconomic outcomes across all gestational ages (left column) and full term only (right column) births.

Psychiatric Problems
Figure DS1. Continued

Socioeconomic Outcomes
We predicted two additional socioeconomic outcomes to examine if we could provide converging evidence with the outcomes predicted in the main analyses. We predicted **low income**, from the LISA database, defined as being in the lowest 20th percentile income bracket for 2 consecutive years. **Higher education** was defined as three or more years of postsecondary education and was gathered from the Education Register. Only offspring born 1973-1983, whose age made it possible to achieve this level of education, were included in this sample.

As can be seen in Figure DS2, below, the baseline and fixed effects findings for these outcomes support those presented in the main analyses; lower birth weight is associated with increased odds of **Low Income** only in baseline analyses. Similar to **Social Welfare Receipt**, the relation was fully attenuated following fixed effects modeling. Low birth weight was also found to decrease the odds of achieving a **Higher Education**, and similar to **Failing Grades** and **Education Under 10 years**, this association was consistent in the fixed effects model.
Sibling-comparison studies assume that findings from families with multiple offspring generalize to families with only one offspring. Therefore, the interpretation of the sibling-comparison results could be confounded if the population-based associations were different in offspring who had siblings than in those that are only children. If systematic magnitude differences are found between offspring with siblings and only children, then the reduction or increase in association magnitude found in the fixed effects models may be due to alternate explanations.

To help assess whether a bias was introduced by analyzing families with multiple offspring, we estimated the population-based estimates between birth weight and offspring outcomes in (a) offspring without siblings and (b) offspring with siblings. Each figure below presents these two baseline models. One model (grey bars with 95% confidence intervals) estimated on the sub-sample of offspring from families with only one offspring within the dataset. The second model (white bars with 95% confidence intervals) was estimated on the sub-sample of offspring from families with more than one child.

Figures DS3 show that the baseline associations are comparable for the two sub-samples of offspring. The figures also suggest that differences between the sub-samples do not account for differences in the sibling-comparison estimates as compared with the population estimates presented in the main paper. Across outcomes, associations in the two sub-samples are in the same direction and the magnitudes of association greatly overlap. Additionally, we found no pattern where magnitudes were always larger in one sub-sample. Overall, this sensitivity analysis suggests that the sibling-comparison results that showed changes in magnitude from the population analyses are not due to different population-based estimates in offspring with siblings than in offspring who are only children.
Figure DS3. Psychiatric Problems
Figure DS3 Continued. Socioeconomic Outcomes
To disentangle the source of possible confounding between birth weight and outcome, we conducted another test that utilizes a population that varies in their genetic relatedness. This was important because of inherent assumptions of the sibling-comparison approach, but also because individual genetic factors account for some variability in birth weight [10, 11]. While siblings share 50% of their genetic makeup on average, cousins, share 12.5% of their genetic makeup on average. Therefore, we examined if the degree to which individuals share genetic risk moderates the association between birth weight and outcomes. If the associations are smaller when comparing relatives that share more genetic background (i.e., sibling associations are smaller than cousin associations), then genetic confounding is implicated. If the associations between birth weight and outcome are found to be the same magnitude across all relative groups, results may instead suggest the importance of environmental confounds. Although cousin versus sibling comparisons cannot by itself support or refute genetic confounding because these groups can also vary on their environmental risk “relatedness”, when these results are combined with results from cousin-comparison designs that also vary in the degree of genetic relatedness, more evidence is gathered.

Figure DS4 show baseline, sibling- and cousin-comparison fixed effect (FE) results. Analyses were performed via stratification on the maternal grandmother of the target child. Overall, results for ASD, psychotic or bipolar disorder, and education under 10 years, support the findings that associations are consistent with a causal inference. For suicide attempt, substance use problem, and criminality, sibling and cousin comparisons similarly fully attenuate the association present in the population baseline analysis. For failing grades, social welfare receipt, it can be noted that the magnitudes of association are greater for cousin comparisons than for sibling comparisons, suggesting genetic confounding.
Figure DS4. Comparison of population baseline, fixed effects sibling-comparison, and fixed effect cousin-comparison for psychiatric morbidity and socioeconomic outcomes.

Psychiatric Problems
Figure DS4 continued. Socioeconomic Outcomes
Additional references

Fetal growth and psychiatric and socioeconomic problems: population-based sibling comparison
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