JAMA Psychiatry | Original Investigation

Association of Fetal Growth With General and Specific Mental Health Conditions

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IMPORTANCE It is unclear if the associations between fetal growth and later mental health conditions remain after controlling for familial factors and psychiatric comorbidity.

OBJECTIVE To examine the associations between fetal growth and general and specific mental health conditions, controlling for familial factors.

DESIGN, SETTING, AND PARTICIPANTS This register-based study conducted in Sweden analyzed 546 894 pairs of full siblings born between January 1, 1973, and December 31, 1998. Sibling pairs were followed up through December 31, 2013. First, population-based and within-sibling pair associations (which controlled for time-invariant familial confounders) between fetal growth and the outcomes were estimated. Second, exploratory factor analysis was applied to the outcomes to derive 1 general factor and 4 specific and independent factors. Third, the general and specific factors were regressed on fetal growth. Statistical analysis was performed from March 27, 2017, to October 27, 2018.

MAIN OUTCOME AND MEASURES The outcomes were 11 psychiatric diagnoses (depression, anxiety, obsessive-compulsive disorder, posttraumatic stress disorder, bipolar disorder, alcohol abuse, drug use, attention-deficit/hyperactivity disorder, autism, schizophrenia, and schizoaffective disorder) and court convictions of violent crimes. Birth weight (in kilograms) statistically adjusted for gestational age was the exposure.

RESULTS The mean (SD) age of the 1 093 788 participants was 27.2 (6.8) years (range, 15.1-40.9 years) and 51.5% were male. Nine outcomes were significantly associated with birth weight in the population at large: depression (odds ratio [OR], 0.96; 95% CI, 0.95-0.98), anxiety (OR, 0.94; 95% CI, 0.92-0.95), posttraumatic stress disorder (OR, 0.91; 95% CI, 0.89-0.93), bipolar disorder (OR, 0.94; 95% CI, 0.89-1.00), alcohol abuse (OR, 0.89; 95% CI, 0.87-0.91), drug use (OR, 0.83; 95% CI, 0.80-0.85), violent crimes (OR, 0.85; 95% CI, 0.83-0.86), attention-deficit/hyperactivity disorder (OR, 0.88; 95% CI, 0.86-0.90), and autism (OR, 0.95; 95% CI, 0.92-0.97). Only depression (OR, 0.95; 95% CI 0.92-0.98), obsessive-compulsive disorder (OR, 0.93; 95% CI, 0.87-0.99), attention-deficit/hyperactivity disorder (OR, 0.86; 95% CI, 0.82-0.89), and autism (OR, 0.72; 95% CI, 0.69-0.76) remained significantly associated within sibling pairs. An exploratory factor analysis indicated that 1 general and 4 specific factors (capturing anxiety, externalizing, neurodevelopmental, and psychotic conditions) fit the outcomes well. Across almost all sensitivity analyses, an increase in birth weight by 1 kg significantly reduced the general (β, −0.047; 95% CI, −0.071 to −0.023) and the specific neurodevelopmental factors (β, −0.159; 95% CI, −0.190 to −0.128) within sibling pairs.

CONCLUSIONS AND RELEVANCE Controlling for familial confounders, reduced fetal growth was associated with a small but significant increase in the general factor of psychopathology and a moderate increase in a specific neurodevelopmental factor.

JAMA Psychiatry. 2019;76(5):536-543. doi:10.1001/jamapsychiatry.2018.4342
Published online February 6, 2019.

Supplemental content

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Reduced fetal growth is associated with an increased level of mental health conditions.[1] Barring a few replication failures,[2,3] reduced fetal growth has been associated with clinical diagnoses of attention-deficit/hyperactivity disorder (ADHD), autism, depression, anxiety, substance abuse, schizophrenia, and bipolar disorder,[4-8] as well as with parent-reported, teacher-reported, and self-reported mental health symptoms.[9-11] These associations are potentially mediated via changes in brain functioning.[12,13]

Two concerns, however, cloud causal interpretations. First, unmeasured genetic or environmental variables might confound the associations.[14] One remedy is to examine whether the associations persist within sibling pairs or twin pairs because they are partly matched on familial time-invariant confounders, including, for example, socioeconomic status and genetics.[15] Whereas the associations between fetal growth and ADHD, autism, and obsessive-compulsive disorder remain associated within sibling and twin pairs,[16-20] the associations with schizophrenia and bipolar disorder appear to attenuate and sometimes become nonsignificant.[18,21,22] Furthermore, the associations between fetal growth and parent-reported externalizing symptoms and substance abuse diagnoses tend to become nonsignificant within sibling pairs.[17,18]

An additional problem is the high degree of overlap among psychiatric disorders.[23-25] An observed association between fetal growth and a given psychiatric condition might be attributed to that which is not shared with other psychiatric phenomena (ie, its unique part), or toward that which is shared with other psychiatric phenomena (ie, comorbidity). Research indicates that psychiatric comorbidity can be explained by a general factor of psychopathology with broad effects on virtually all forms of mental health conditions.[26-28] For example, in a sample of more than 35 000 US adults who were administered a psychiatric interview, a model of comorbidity that included a general factor fit the data significantly better.[29] Supporting the effect of fetal growth on psychiatric comorbidity, in a co-twin control study of 745 twin pairs, the twin who weighed less at birth was rated as having a significantly higher score on the total problem scale of the Child Behavior Checklist, which is an approximation of the general factor, in childhood and adolescence.[30]

However, it remains unknown whether fetal growth is associated with a general factor of psychopathology based on more severe clinical diagnoses, and whether the associations with the unique parts of disorders persist after isolating the general factor. The purpose of this study was to examine the influence of fetal growth on both general and specific mental health conditions, as indicated by clinical diagnoses, across the adult age spectrum in a large population-based sample of full sibling pairs.

Key Points

Question Do the associations between fetal growth and later mental health conditions remain after controlling for familial confounding factors and psychiatric comorbidity?

Findings This register-based study including more than 1 million participants and using a within-sibling pair design found that higher birth weight (statistically adjusted for gestational age) significantly lowered the risk for attention-deficit/hyperactivity disorder, autism, obsessive-compulsive disorder, and depression. Furthermore, an increase in birth weight by 1 kg significantly decreased a general factor of psychopathology by 0.047 SDs and a specific neurodevelopmental factor by 0.159 SDs.

Meaning After controlling for familial factors and psychiatric comorbidity, fetal growth was most strongly associated with specific neurodevelopmental disorders.

Methods

Participants

We linked together all Swedish individuals born between January 1, 1973, and December 31, 1998, from the Swedish Medical Birth Register, Multi-Generation Register, the National Inpatient Register and National Outpatient Register (the inpatient register captures diagnoses since 1973, and the outpatient register captures diagnoses since 2001), and the National Crime Register. The individuals were followed up through December 31, 2013. After excluding individuals who had died or migrated, we selected the oldest full sibling pair (ie, individuals who had the same biological mother and father) within each family to maximize the follow-up time (and thereby power). Because Swedish full siblings almost always grow up in the same household,[31] they are more likely to have experienced a similar shared environment. We included only full siblings who were born within 5 years of each other to maximize the probability that the shared environment remained similar for the pairs (see eTable 8 in the Supplement for other age cutoffs). The final sample consisted of 546 894 pairs of full siblings. The mean (SD) age was 27.2 (6.8) years (range, 15.1-40.9 years) and 51.5% were male. This study was approved by the Regional Ethical Review Board in Stockholm. Because the study relied on deidentified registry data, informed consent was not required.

Measures

For the exposure, as a measure of fetal growth, we focused on birth weight (in kilograms) statistically adjusted for gestational age. As covariates, we included sex, date of birth, and birth order. For the outcomes, we included inpatient and outpatient diagnoses of depression, anxiety, obsessive-compulsive disorder, posttraumatic stress disorder, bipolar disorder, alcohol abuse, drug use, ADHD, autism spectrum disorder, schizophrenia, and schizoaffective disorder assigned by the attending psychiatrist in accord with versions 8, 9, or 10 of the *International Classification of Diseases* (eTable 1 in the Supplement).[32] Diagnoses were recorded as lifetime prevalence rates; thus, participants could receive a different diagnosis at any point. We included only diagnoses assigned at age 12 years or later, except for autism and ADHD, which were limited to age 2 years or later. As a marker of antisocial behavior, we included court convictions of violent crimes (eg, unlawful threats, assault, and homicide), which can occur from age 15 years. We counted only the first instance of diagnoses and court convictions (ie, we treated the data as binary). Descriptive statistics about the exposure, covariates, and outcomes are displayed in eTable 2 in the Supplement.

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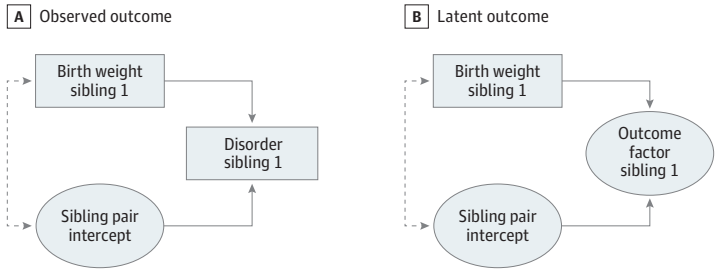
Figure 1. Observed Outcome and Latent Outcome, Regressed on Birth Weight



A, Observed outcome. B, Latent outcome. Absence of dashed line indicates random-effects model. Presence of dashed line indicates fixed-effects model.

Statistical Analysis

Statistical analysis was performed from March 27, 2017, to October 27, 2018. We analyzed the data in wide format in a Structural Equation Modeling (SEM) framework, which featured several advantages. First, SEM allows for analyzing multiple outcomes simultaneously, such that we could separate specific from general variance at the outcome level. Second, SEM allows for analyzing error-free latent (unobserved) factors rather than partly unreliable outcomes, such that decreases in the fixed-effects estimates cannot be attributed to measurement error in the outcomes. Third, because only pairs who are discordant for the outcomes contribute to the fixed-effect estimates, analyzing latent factors that consist of several variables increases the number of discordant pairs and thereby increases the power. However, SEM is also disadvantageous in that it is a computational challenge to model the hazard ratio of multiple outcomes simultaneously. Therefore, we only modeled whether the outcome had occurred (ie, we treated the data as ordered categories, assuming that an underlying normal and continuous probability function underlay the observed binary outcomes). All analyses were conducted with Mplus software (Muthén and Muthén) using the mean-adjusted and variance-adjusted weighted least square estimator.[33] All confidence intervals were 2-sided.

Bivariate Analyses: Random- and Fixed-Effects Regression

We assumed that part of the variation in the risk for each outcome could be attributed partly to a normally distributed latent sibling pair intercept (ie, a familial effect). We regressed each disorder onto birth weight (adjusted for gestational age) and the covariates in 2 ways following the hybrid approach by Allison[34] (**Figure 1**A). First, to emulate a random-effects model, we forced the latent sibling pair intercept to be unrelated to birth weight and the covariates. This model assumes that the average degree of mental conditions in each sibling pair is unrelated to their birth weight (which would be violated if, for example, poverty or genetics led to both lower birth weight and a higher degree of mental health conditions in the pairs). Second, to emulate a fixed-effects regression model, we allowed the latent sibling pair intercept to correlate with birth weight and the covariates, thereby controlling for all time-invariant unmeasured confounders shared within sibling pairs. In other words, this model estimates whether an individual with low birth weight has an increased (or decreased) risk of developing later mental health conditions, controlling for the overall degree of mental health conditions in the sibling pair. Thus, this model controls for all unmeasured confounders shared between siblings (eg, poverty or genetics) that might lead them to have both lower birth weight and more mental health conditions compared with other sibling pairs.

Multivariate Analyses: Random- and Fixed-Effects Regression

We conducted an exploratory factor analysis on the 12 outcomes to examine whether a fewer number of latent continuous factors could account for their overlap. We used exploratory factor analysis rather than confirmatory approaches because we did not have a strong intuition about how the disorders with psychotic or neurodevelopmental features might pertain to the internalizing and externalizing disorders, and because the outcomes seemed unlikely to have simple structure. We used the scree plot to determine how many factors to extract[35] and used the bifactor rotation to isolate general from specific variance.[36,37] This generates a single general factor that captures the comorbidity among all the outcomes and a set of specific factors that captures unique variance shared only among a subset of the outcomes. Importantly, the general factor is uncorrelated with the specific factors, such that potential associations between fetal growth and the specific factors cannot be attributed to general comorbidity. We computed the explained common variance index to quantify how much of the reliable variance in the adverse outcomes was attributable to the general factor.[38]

Second, we regressed the latent and continuous general and specific factors onto birth weight (adjusted for gestational age) and the covariates within the SEM framework.[39] We emulated the random and fixed effects by assuming that part of the variation in each latent factor could be partly attributed to a sibling pair intercept (Figure 1B; see eFigure 1 in the Supplement for a more complete figure of the multivariate random and fixed model).[37] We allowed the means and intercepts to vary between the older and younger siblings, but held all other parameters (ie, variances and covariances) equal between the siblings. Because past research has indicated that some of the associations between fetal growth and psychiatric disorders appear nonlinear,[18] we included both centered birth weight and birth weight squared as the exposures.

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Results

Bivariate Regressions

Reduced fetal growth significantly increased the risk for 9 of the 12 outcomes: depression (odds ratio [OR], 0.96; 95% CI, 0.95-0.98), anxiety (OR, 0.94; 95% CI, 0.92-0.95), posttraumatic stress disorder (OR, 0.91; 95% CI, 0.89-0.93), bipolar disorder (OR, 0.94; 95% CI, 0.89-1.00), alcohol abuse (OR, 0.89; 95% CI, 0.87-0.91), drug use (OR, 0.83; 95% CI, 0.80-0.85), violent crimes (OR, 0.85; 95% CI, 0.83-0.86), attention-deficit/hyperactivity disorder (OR, 0.88; 95% CI, 0.86-0.90), and autism (OR, 0.95; 95% CI, 0.92-0.97) (**Table 1**). When compared within sibling pairs, that is, after controlling time-invariant familial unmeasured confounders, higher birth weight decreased the risk for depression (OR, 0.95; 95% CI, 0.92-0.98), obsessive-compulsive disorder (OR, 0.93; 95% CI, 0.87-0.99), ADHD (OR, 0.86; 95% CI, 0.82-0.89), and autism (OR, 0.72; 95% CI, 0.69-0.76) (Table 1).

Multivariate Regressions

To examine whether the bivariate associations could be attributed to variance specific to each condition vs that accounted for by the general factor, we examined the multivariate structure of the 12 outcomes. The first 10 eigenvalues are 5.81, 1.35, 1.11, 0.99, 0.60, 0.55, 0.45, 0.34, 0.27, and 0.23, indicating an elbow at 4 factors (see eFigure 2 in the Supplement for the scree plot). However, because we wanted to model the general factor in addition to specific factors, we extracted an additional fifth factor (but we also performed the analyses using a 4-factor solution; eTables 3 and 4 in the Supplement). The 5-factor solution fit the data well (root mean square error of approximation [RMSEA] = 0.005; 90% CI, 0.005-0.006; confirmatory fit index [CFI] = 0.999; Tucker-Lewis index [TLI] = 0.997; χ^2_{16} = 545.222; P < .001), which we rotated toward 1 general and 4 specific factors.[37,40]

As displayed in **Table 2**,[38] all outcomes had large loadings on the general factor (mean loading, 0.65; range, 0.35-0.87). The first specific factor captured anxiety disorders (obsessive-compulsive disorder loading, 0.49; and anxiety loading, 0.33). The second specific factor captured externalizing conditions (violent crimes loading, 0.57; drug use loading, 0.59; and alcohol abuse loading, 0.47). The third specific factor captured neurodevelopmental disorders (ADHD loading, 0.54; and autism loading, 0.59). The fourth specific factor captured psychotic disorders (schizophrenia loading, 0.68; and schizoaffective loading, 0.54).

We then regressed the general and specific factors onto birth weight (adjusted for gestational age) and the covariates, which fit the data well (RMSEA = 0.011; 90% CI, 0.011-0.011; CFI = 0.985; TLI = 0.984; χ^2_{511} = 34 688.460; P < .001). Fetal growth was associated with the general and the specific factors (**Table 3**). The significant effect of birth weight squared indicated that risk was primarily elevated for low birth weight but not for medium or high birth weight (**Figure 2**).

We then controlled time-invariant familial unmeasured confounders, which also fit the data well (RMSEA = 0.011; 90% CI, 0.011-0.011; CFI = 0.986; TLI = 0.983; χ^2_{486} = 34 010.355; P < .001). Within sibling pairs, higher birth weight was significantly associated with lower scores on the general (β, −0.047; 95% CI, −0.071 to −0.023; Figure 2A), specific anxiety (β, −0.059; 95% CI, −0.114 to −0.004; Figure 2B), and specific neurodevelopmental factors (β, −0.159; 95% CI, −0.190 to −0.128; Figure 2D), as well as with higher scores on the specific externalizing factor (β, 0.033; 95% CI, 0.002-0.064; Figure 2C).

Table 1. Psychiatric Disorders and Criminality Regressed on Birth Weight Coded in Kilograms, Controlling for Gestational Age

	Odds Ratio (95% CI)	
Outcome	Random Effect	Fixed Effect
Depression	0.96 (0.95-0.98)[a]	0.95 (0.92-0.98)[b]
Anxiety	0.94 (0.92-0.95)[a]	1.00 (0.97-1.03)
OCD	1.03 (0.99-1.07)	0.93 (0.87-0.99)[c]
PTSD	0.91 (0.89-0.93)[a]	0.98 (0.94-1.02)
Bipolar disorder	0.94 (0.89-1.00)[d]	0.98 (0.92-1.05)
Alcohol abuse	0.89 (0.87-0.91)[a]	0.97 (0.94-1.01)
Drug use	0.83 (0.80-0.85)[a]	0.97 (0.93-1.02)
Violent crimes	0.85 (0.83-0.86)[a]	0.97 (0.93-1.00)
ADHD	0.88 (0.86-0.90)[a]	0.86 (0.82-0.89)[a]
Autism	0.95 (0.92-0.97)[a]	0.72 (0.69-0.76)[a]
Schizophrenia	0.97 (0.90-1.04)	0.89 (0.78-1.02)
Schizoaffective disorder	1.06 (0.96-1.17)	1.13 (0.89-1.42)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder.

[a] P < .001.

[b] P = .001.

[c] P = .03.

[d] P = .04.

Sensitivity Analyses

In the eAppendix in the Supplement, we examined (1) whether the associations with fetal growth remained similar when extracting 4 instead of 5 factors (eTables 3 and 4 in the Supplement); (2) whether changes in diagnostic procedures might have influenced the results by analyzing only individuals born after 1987, such that they were at least 10 years of age when the *ICD-10* was introduced (eTable 5 in the Supplement); (3) whether the results were driven primarily by premature births (eTable 6 in the Supplement); (4) whether the results generalized to clinical cutoffs of fetal growth (eTable 7 in the Supplement); (5) whether the results were consistent for siblings born within 2.51, 3, 4, 6, 7, 8, 9, and 10 years apart (eTable 8 in the Supplement); (6) whether the results were similar for same-sex sibling pairs (eTable 9 in the Supplement); and (7) whether the results were comparable among those born within 3 SDs of the mean of birth weight and gestational age (eTable 10 in the Supplement).

Across all 7 sensitivity analyses, restricted fetal growth was significantly associated with higher scores on the specific neurodevelopmental factor within sibling pairs. Likewise, restricted fetal growth was associated with higher scores on the general factor across 6 of the 7 sensitivity analyses (the association approached but failed to reach conventional levels of statistical significance for siblings born within 2.51 years). The

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Table 2. Exploratory Factor Analysis Factor Loadings After Bifactor Rotation

Outcome	General Factor[a]	Specific Anxiety Factor	Specific Externalizing Factor	Specific Neurodevelop-mental Factor	Specific Psychotic Factor
Depression	0.87	0.11	−0.05	−0.13	−0.18
Anxiety	0.79	0.33	0.06	−0.09	−0.16
OCD	0.59	0.49	−0.15	0.11	0.02
PTSD	0.69	0.08	0.09	−0.17	−0.18
Bipolar disorder	0.78	−0.07	−0.05	−0.10	0.00
Alcohol abuse	0.49	0.01	0.47	−0.10	−0.02
Drug use	0.67	0.03	0.59	−0.05	0.00
Violent crimes	0.35	−0.10	0.57	0.10	0.05
ADHD	0.66	−0.07	0.20	0.54	−0.20
Autism	0.59	0.11	−0.15	0.59	0.08
Schizophrenia	0.62	0.10	0.07	0.04	0.68
Schizoaffective disorder	0.74	−0.24	−0.09	−0.16	0.54

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder.

[a] Explained common variance = 0.63.[38]

Table 3. Standardized General and Specific Factors Regressed on Birth Weight Coded in Kilograms, Controlling for Gestational Age

Factor	Random Effect (95% CI)		Fixed Effect (95% CI)	
	Birth Weight β	Birth Weight Squared β	Birth Weight β	Birth Weight Squared β
General factor	−0.043 (−0.057 to −0.029)[a]	0.033 (0.023 to 0.043)[a]	−0.047 (−0.071 to −0.023)[a]	0.033 (0.017 to 0.049)[a]
Specific anxiety factor	−0.034 (−0.063 to −0.005)[b]	−0.004 (−0.026 to 0.018)	−0.059 (−0.114 to −0.004)[c]	−0.023 (−0.060 to 0.014)
Specific externalizing factor	−0.115 (−0.133 to −0.097)[a]	−0.040 (−0.054 to −0.026)[a]	0.033 (0.002 to 0.064)[c]	−0.046 (−0.068 to -0.024)[a]
Specific neurodevelopmental factor	−0.050 (−0.068 to −0.032)[a]	0.068 (0.056 to 0.080)[a]	−0.159 (−0.190 to −0.128)[a]	0.053 (0.031 to 0.075)[a]
Specific psychotic factor	0.042 (0.007 to 0.077)[b]	−0.013 (−0.038 to 0.012)	0.001 (−0.066 to 0.068)	0.006 (−0.051 to 0.039)

[a] $P < .001$.

[b] $P = .02$.

[c] $P = .04$.

observation that reduced fetal growth increased the risk for anxiety but lowered the risk for externalizing conditions failed to emerge consistently across the sensitivity analysis.

Discussion

Reduced fetal growth had a small but significant effect on the risk of developing several psychiatric disorders in adulthood. After controlling for time-invariant unmeasured confounders shared by full sibling pairs, only the associations with ADHD, autism, obsessive-compulsive disorder, and depression remained statistically significant. Depression, however, was subsumed by the general factor, partly in line with past research,[28,41] highlighting the importance of taking comorbidity into account when studying mental health conditions.[27] In the within-pair multivariate analyses, reduced fetal growth was significantly associated with higher scores on the general and, to a greater extent, the specific neurodevelopmental factors.

Replicating past research, we found that the covariation among psychiatric disorders could be partly accounted for by a general factor.[26-29] Whereas twin, sibling, and molecular genetic investigations have highlighted its genetic cause,[31,41,42] our study replicated a co-twin control study, which found an association of fetal growth with total symptom score in adolescence,[30] and extended it to a general factor based on more severe mental health conditions in adulthood. Thus, fetal growth seems to mediate environmental effects also to the general factor, albeit weakly. One speculation is that reduced fetal growth compromises brain development during a critical period,[43] which in turn slightly increases the risk not only for neurodevelopmental disorders but also for virtually all mental health conditions.

Restricted fetal growth had the strongest association with the specific neurodevelopmental factor. It has been proposed that the association between reduced fetal growth and ADHD are preceded by an insufficient supply of oxygen and nutrients for the developing fetus[44]; our results imply that this pathway might be shared across the neurodevelopmental spectrum. Multiple studies have found that reduced fetal growth is associated with both autism and ADHD.[16-18,20] Because several twin studies of neurodevelopmental symptoms have indicated that a portion of their overlap can be attributed to nonfamilial sources,[45-47] a speculation is that fetal growth is one such source.

Although we failed to identify an association between restricted fetal growth and psychotic disorders within sibling pairs, this null finding is in line with previous co-siblings control studies. For example, in a study of Swedish twins and

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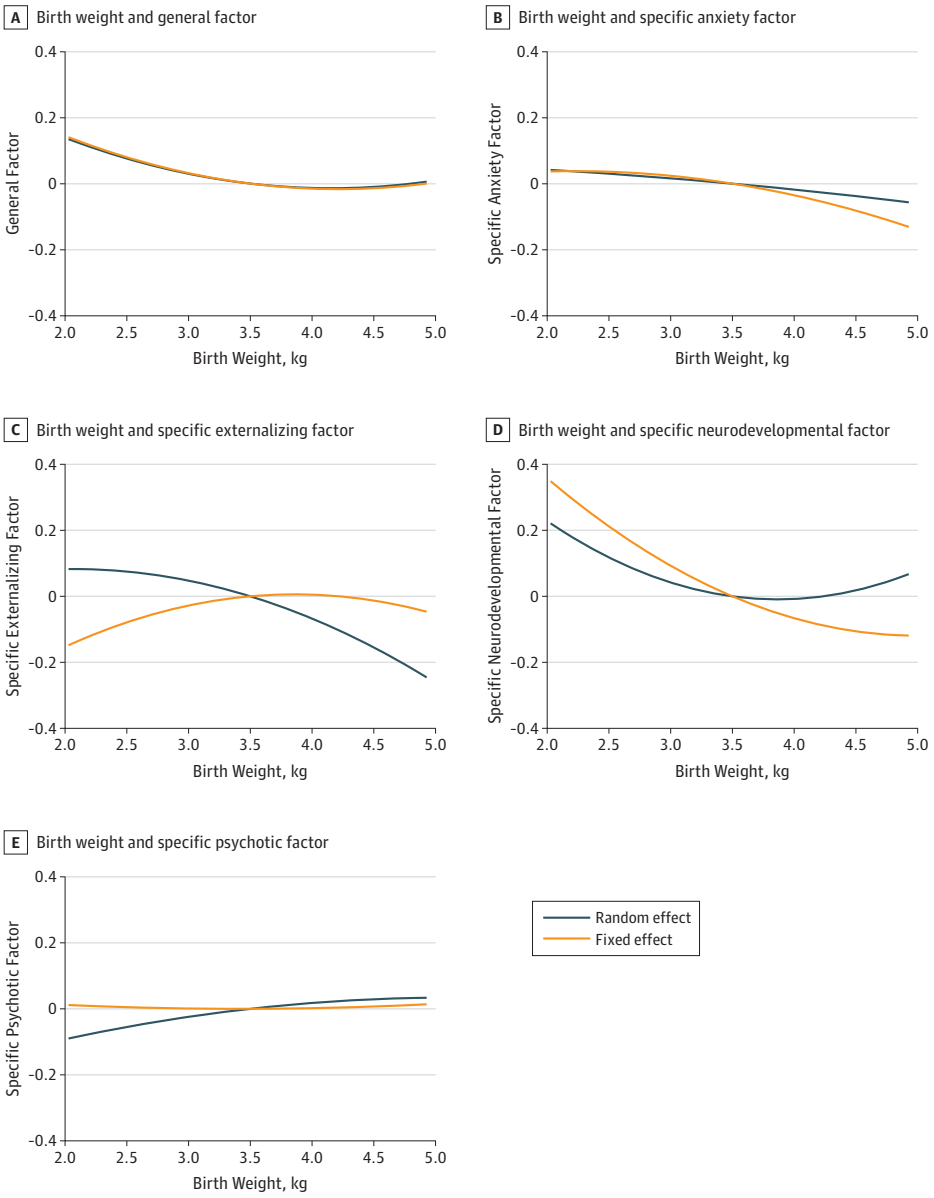
Figure 2. Association Between Birth Weight and General and Specific Factors



A, Association between birth weight and the general factor. B, Association between birth weight and the specific anxiety factor. C, Association between birth weight and the specific externalizing factor. D, Association between birth weight and the specific neurodevelopmental factor. E, Association between birth weight and the specific psychotic factor. All factors are measured in standardized units. See Table 3 for the 95% CIs.

a study of Danish siblings the within-pair associations between reduced fetal growth and schizophrenia became nonsignificant.[21,22] With the caveat that this estimate tends to be relativity imprecise given the rarity of the condition, one speculation is that reduced fetal growth might not be in the causal pathway leading to psychotic disorders after adjusting for comorbidity and familial confounding.

Because the associations remained after controlling for time-invariant familial unmeasured confounders, interventions geared toward increasing fetal growth might reduce future general and specific neurodevelopmental disorders. However, treatment options for fetal growth are limited and tend to have a small effect.[48-50] Because the effect sizes presented herein were small, in line with past research,[17,51] potential interventions are likely to have a relatively small effect on later psychiatric conditions. Nevertheless, given the sheer prevalence of mental health conditions,[24] combating maternal malnourishment and improving prenatal care still might influence a significant number of cases.[52]

Limitations

This study has some limitations. First, it is a computational challenge to model the hazard ratio of multiple outcomes simultaneously within a SEM framework. Therefore, we assumed that the overlap among the diagnoses could be accounted for by unobserved and continuous factors. Thus, we modeled only whether the events occurred, but not their rate of onset as a function of time.

Second, although restricted fetal growth increased the risk for anxiety but lowered the risk for externalizing conditions,

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the association was not consistent across all sensitivity analyses. Therefore, it remains uncertain whether fetal growth is a risk factor for externalizing and internalizing conditions in this population.

Third, the registers only capture individuals who have been diagnosed by specialists, which usually occurs after referral from the primary care system. Therefore, we were limited to analyzing associations with more severe forms of mental conditions. Less-troubled individuals who do not necessarily warrant referral to specialists might be included in future studies.[53]

Fourth, although we used siblings born within 5 years of one another to maximize environmental matching, we did not control unmeasured confounders not shared by sibling pairs. Other types of quasi-causal designs relying on different assumptions might begin to address this concern.[14] Furthermore, we used full (compared with half) siblings to maximize genetic matching; nevertheless, only identical twins can provide complete genetic matching.

Conclusions

In this population-based sample, reduced fetal growth was associated with a small but significant increased risk for several psychiatric disorders. However, many of these associations became nonsignificant within full sibling pairs. After controlling for comorbidity, restricted fetal growth most strongly increased the risk for neurodevelopmental disorders.

ARTICLE INFORMATION

Accepted for Publication: November 13, 2018.

Published Online: February 6, 2019. doi:10.1001/jamapsychiatry.2018.4342

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Author Contributions: Dr Pettersson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Pettersson, Larsson, Lichtenstein.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Pettersson.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Pettersson.
Obtained funding: Larsson, D'Onofrio, Almqvist, Lichtenstein.
Administrative, technical, or material support: Lichtenstein.
Supervision: Larsson.

Conflict of Interest Disclosures: Dr Larsson reported serving as a speaker for Eli Lilly and Shire and receiving a research grant from Shire. Dr Lichtenstein reported serving as a speaker for Medice. No other disclosures were reported.

Funding/Support: Financial support was provided from the Swedish Research Council through the Swedish Initiative for Research on Microdata in the Social and Medical Sciences (SIMSAM) framework grant 340-2013-5867.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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