Supplementary Online Content

Pettersson E, Larsson H, D'Onofrio B, Almqvist C, Lichtenstein P. Association of fetal growth with general and specific mental health conditions. *JAMA Psychiatry.* Published online February 6, 2019. doi:10.1001/jamapsychiatry.2018.4342

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. *International Classification of Diseases* (*ICD*) Codes			
Diagnosis	ICD-8	ICD-9	ICD-10
Depression	300.4	311; 300.e	F32-F39
Anxiety	300 (excl. 300.3, 300.4)	300 (excl. 300.e, 300.d)	F40-41, F44-45, F48
OCD	300.3	300.d	F42
PTSD	307	308, 309	F43
Bipolar	296.0-296.3, 296.7, 296.8	296.a-296.e, 296.w, 296.x	F30, F31
Alcohol	303, 291	291, 303, 305.a	F10 (excl. F10.5)
Drugs	304	292, 304, 305.x (excl. 305.a),	F11-19 (excl. F11-19.x)
ADHD	-	314	F90
Autism	-	299	F84 (excl. F84.2)
Schizophrenia	295.0-295.4, 295.6, 295.8-295.9	295.a-295.e, 295.g, 295.w, 295.x	F20
Schizoaffective	295.7	295.h	F25

Note. OCD = Obessive-compulsive disorder; PTSD = Post-traumatic stress disorder; ADHD = Attention-deficit/Hyperactivity disorder.

eTable 2. Descriptive Statistics about Exposure, Covariates, and Outcomes

	Mean	SD	Prevalence (%)
Birth weight (kilos)	3.53	0.53	-
Gestational age (weeks)	39.53	1.74	-
Age	27.18	6.83	-
Sex (male)	-	-	51.49
Small for gestational age	-	-	2.75
Depression	-	-	4.89
Anxiety	-	-	5.05
OCD	-	-	0.68
PTSD	-	-	2.18
Bipolar	-	-	0.70
Alcohol	-	-	2.85
Drugs	-	-	1.51
Violent crimes	-	-	2.76
ADHD	-	-	2.31
Autism	-	-	1.11
Schizophrenia	-	-	0.14
Schizoaffective	-	-	0.06

Note. SD = standard deviation. OCD = Obsessive-compulsive disorder; PTSD = Post-traumatic stress disorder; ADHD = Attention-deficit/Hyperactivity disorder.

eAppendix. Sensitivity Analyses

Sensitivity analysis 1: Four-factor solution

We conducted seven sensitivity analyses to examine whether the results were consistent across different conditions. First, although we opted to extract five factors, the scree plot supported fewer factors. Therefore, we repeated the multivariate fixed effects regressions, but after extracting only four factors, which also fit the data well (Root Mean Square Error of Approximation, RMSEA = .008, 90% CI: .007, .008; Confirmatory Fit Index, CFI = .998; Tucker-Lewis Index, TLI = .994; χ^2 = 1557.182, degrees of freedom, df = 24, p < .001). We then rotated the four factors toward one general factor and three specific factors (eTable 3). As before, all outcomes had large loadings on the general factor (mean loading = .66, range = .42, .86). The first specific factor captured neurodevelopmental problems (ADHD loading = .47; and autism loading = .64). The second specific factor captured obsessive-compulsive disorder at one end (OCD loading = -.33), and externalizing problems at the opposite end (violent crimes loading = .55; drug loading = .46; and alcohol loading = .36). The third specific factor captured psychotic problems (schizophrenia loading = .66; schizoaffective loading = .71).

We then regressed the general and three specific factors onto birth weight and the covariates within a fixed effect format, which fit the data well (RMSEA = .011, 90% CI: .011, .011; CFI = .985; TLI = .983; χ^2 = 34639.282, df = 497, p < .001). As displayed in eTable 4, within sibling pairs, that is, after controlling time-invariant familial confounds, higher birth weight significantly predicted lower scores on the general (β = -.050, 95% CI: -.066, -.034) and specific neurodevelopmental factors (β = -.163; 95% CI: -.192, -.134), as well as higher scores on the specific externalizing factor (β = .029; 95% CI: .002,.056). Thus, on the whole, the four- and five-factor solutions appeared to generate very similar results, such that the effect of fetal growth on mental health problems does not appear to depend on the number of extracted factors.

Sensitivity analysis 2: ICD-10 only

Second, to examine whether changes in diagnostic procedures might have influenced the results, we analyzed a subsample of individuals born after 1987, such that they were at least ten years old when the ICD-10 was introduced. We re-ran the multivariate fixed effect model using this subsample, which fit the data well (RMSEA = .014, 90% CI: .014, .014; CFI = .978; TLI = .975; χ^2 = 24487.580, *df* = 486, $p < .001$). As displayed in eTable 5, within sibling pairs, low birth weight significantly predicted the general (β = -.048, 95% CI: -.087, -.009), the specific neurodevelopmental (β = -.175, 95% CI: -.220, -.130), and the specific anxiety factors (β = -.141, 95% CI: -.231, -.051). Thus, the results were by and large consistent with the analyses based on the complete sample, indicating that the results do not vary based on diagnostic procedures.

Sensitivity analysis 3: Full-term births

Third, to examine if the results were primarily driven by premature births, we restricted the analyses to those born at full term, that is, at week 37 or later. This model fit the data well (RMSEA = .014, 90% CI: .014, .014; CFI = .974; TLI = .970; χ^2 = 43993.957, *df* = 486, $p <$ .001). As displayed in eTable 6, within sibling pairs, lower birth weight predicted higher scores on the general (β = -.043, 95% CI: -.068, -.018), specific anxiety (β = -.063, 95% CI: -.126, .000), and specific neurodevelopmental factors (β = -.116, 95% CI: -.151, -.081). Thus, on the whole, the results were comparable to those based on the complete sample, indicating that premature births do not appear to drive the results.

Sensitivity analysis 4: Binary diagnosis of small for gestational age

Fourth, to examine if the results would generalize to clinical cutoffs, we regressed the general and specific factors on a binary small for gestational age variable (SGA; 0 = not

SGA; 1 = SGA). This model fit the data well (RMSEA = .008, 90% CI: .008, .008; CFI = .982; TLI = .980; χ^2 = 12657.994, *df* = 394, *p* < .001). As displayed in eTable 7, within exposure-discordant sibling pairs, those who were born small for gestational age scored higher on the general (β = .031; 95% CI: .013, .049) and the specific neurodevelopmental factors (β = .037; 95% CI: .012, .062), as well as lower on the specific externalizing factor (β = -.027; 95% CI: -.051, -.003) compared to their sibling. Thus, compared to the original solution in which we treated birth weight as a continuous variable, the effect of restricted fetal growth, when coded as a clinical and binary diagnosis, remained significantly associated with the general and specific neurodevelopmental factors.

Sensitivity analysis 5: Including siblings born between the median (2.51) and up to 10 years apart

Although we a priori decided to only include siblings who were born within five years of each other to maximize the probability that they had experienced a similar shared environment, this particular cut-off was arbitrary. Therefore, we re-ran the analyses with additional cut-offs. In the original sample, the median age difference between siblings was 2.51 years. To examine if the results were consistent for individuals born closer in age, who might arguably have been more likely to experience a more similar shared environment, we re-ran the analyses including only individuals born within 2.51 years or less of each other. We then continued to examine whether the associations differed across increasing 1-year intervals, ranging from siblings born up to 3 years apart, to siblings born up to 10 years apart (excluding 5 years apart, which we relied on in the original analyses).

As displayed in eTable 8, higher birth weight significantly predicted lower scores on the specific neurodevelopmental factor across all age cutoffs (mean β = -.147). Furthermore, higher birth weight significantly predicted lower scores on the general factor across all age cutoffs (mean β = -.043) except for those born within 2.51 years apart. For that particular age cutoff, the association approached conventional levels of statistical significance (β = -.027; 95% CI: -.060, .006).

Thus, the results appear very similar regardless of whether we restricted the siblings to be born anywhere between 2.51 and 10 years apart. However, when analyzing only siblings born within 2.51 years apart, the association between higher birth weight and lower scores on the general factor no longer reached conventional levels of statistical significance. This could have occurred because siblings born closer in age experience a more similar shared environment, which in turn was better controlled for in the analyses where the sibling pairs were closer in age, or because this subsample was smaller (leading to larger standard errors).

Sensitivity analysis 6: Analyzing sex-concordant pairs separately

Although we included sex as a covariate in all analyses, it is possible that the sex-discordant pairs were not comparable to the sex-concordant pairs. We therefore examined only sex-concordant pairs to see if the results were consistent with that of the complete sample. Both the male-concordant subsample (RMSEA = .011, 90% CI: .011, .011; CFI = .984; TLI = .982; χ^2 = 8654.732, *df* = 434, $p < .001$) and the female- concordant subsample (RMSEA = .011, 90% CI: .011, .011; CFI = .988; TLI = .986; χ^2 = 7397.803, *df* = 434, $p < .001$) fit the data well. As displayed in eTable 9, for both male- and female-concordant pairs, higher birth weight significantly predicted lower scores on the general (male pair β = -.059, 95% CI: -.108, -.010; female pair β = -.083, 95% CI: -.130, -.036) and specific neurodevelopmental factors (male pair β = -.107, 95% CI: -.168, -.046; female pair β = -.116, 95% CI: -.190, -.042). Thus, on the whole, the sex-concordant pairs evidenced similar patterns of associations as that of the complete sample, at least in terms of lower birth weight increasing the scores on the general and specific neurodevelopmental factors, indicating that those results do not appear to hinge on particular sex-dyads.

Sensitivity analysis 7: Analyzing individuals born within three standard deviations of the mean of birth weight and gestational age

Because the purpose of the study was to examine the effect of reduced fetal growth on mental health problems, we did not exclude outliers. However, to ensure that the results were robust after excluding outliers, we re-ran the analyses including only those born within three standard deviations of the mean of birth weight (i.e., between 1.94 and 5.12 kilograms) and gestational age (i.e., between 34.41 and 44.75 weeks). The model based on this subsample fit the data well (RMSEA = .009, 90% CI: .008, .009; CFI = .984; TLI = .982; χ^2 = 18562.028, *df* = 486, $p < .001$).

As displayed in eTable 10, the results were similar to those based on the full sample in that higher birth weight predicted lower scores on the general (β = -.046, 95% CI: -.070, -.022) and the specific neurodevelopmental (β = -.139, 95% CI: -.172, -.106). Thus, including versus excluding birth weight and gestational age outliers did not appear to change the results.

eTable 3. EFA Loadings After Bifactor Rotation of Four Factors				
Outcome	General factor	Specific neurodevelopmental factor	Specific externalizing factor	Specific psychotic factor
Depression	**0.86**	-0.11	-0.20	-0.02
Anxiety	**0.83**	-0.10	-0.16	-0.09
OCD	**0.55**	0.11	**-0.33**	0.01
PTSD	**0.71**	-0.18	-0.06	-0.07
Bipolar	**0.74**	-0.06	-0.11	0.16
Alcohol	**0.55**	-0.17	**0.36**	-0.03
Drugs	**0.75**	-0.13	**0.46**	0.01
Crimes	**0.42**	0.02	**0.55**	0.01
ADHD	**0.69**	**0.47**	0.18	-0.14
Autism	**0.57**	**0.64**	-0.14	0.08
Schizophrenia	**0.56**	0.11	0.06	**0.66**
Schizoaffective	**0.61**	-0.07	-0.05	**0.71**

Note. Loadings equal to or greater than |0.30| are bolded. OCD = Obsessive-compulsive disorder; PTSD = Post-traumatic stress disorder; ADHD = Attention-deficit/Hyperactivity disorder.

eTable 4. Standardized General and Specific Factors Based on Four-Factor Solution Regressed on Birth Weight Coded in Kilograms Controlling Gestational Age

	Fixed effect	
Factor	Birth weight beta	Birth weight^2 beta
General factor	**-0.050** (-0.066, -0.034)	**0.024** (0.014, 0.034)
Specific neurodevelopmental	**-0.163** (-0.192, -0.134)	**0.063** (0.043, 0.083)
Specific externalizing	**0.029** (0.002, 0.056)	**-0.037** (-0.055, -0.019)
Specific psychotic	0.038 (-0.035, 0.111)	-0.010 (-0.061, 0.041)

Note. 95% confidence intervals in parentheses. Betas significant at $p < .05$ are bolded.

eTable 5. Standardized General and Specific Factors Regressed on Birth Weight Coded in Kilograms Controlling Gestational Age Among Those Born 1987 or Later

	Fixed effect	
Factor	Birth weight beta	Birth weight^2 beta
General factor	**-0.048** (-0.087, -0.009)	**0.040** (0.015, 0.065)
Specific anxiety	**-0.141** (-0.231, -0.051)	-0.005 (-0.060, 0.050)
Specific externalizing	0.026 (-0.027, 0.079)	**-0.069** (-0.102, -0.036)
Specific neurodevelopmental	**-0.175** (-0.220, -0.130)	**0.067** (0.038, 0.096)
Specific psychotic	-0.020 (-0.142, 0.102)	-0.004 (-0.077, 0.069)

Note. 95% confidence intervals in parentheses. Betas significant at $p < .05$ are bolded.

eTable 6. Standardized General and Specific Factors Regressed on Birth Weight Coded in Kilograms Controlling Gestational Age Among those Born at Week 37 or Later

	Fixed effect	
Factor	Birth weight beta	Birth weight^2 beta
General factor	**-0.043** (-0.068, -0.018)	0.015 (-0.010, 0.040)
Specific anxiety	**-0.063** (-0.126, 0.000)	-0.031 (-0.090, 0.028)
Specific externalizing	0.023 (-0.012, 0.058)	**-0.043** (-0.076, 0.010)
Specific neurodevelopmental	**-0.116** (-0.151, -0.081)	**0.044** (0.011, 0.077)
Specific psychotic	0.013 (-0.061, 0.087)	-0.064 (-0.137, 0.009)

Note. 95% confidence intervals in parentheses. Betas significant at $p < .05$ are bolded.

eTable 7. Standardized General and Specific Factors Regressed on Small for Gestational Age (SGA) Diagnosis	
	Fixed effect
Factor	Beta
General	**0.031** (0.013, 0.049)
Specific anxiety	0.001 (-0.042, 0.044)
Specific externalizing	**-0.027** (-0.051, -0.003)
Specific neurodevelopmental	**0.037** (0.012, 0.062)
Specific psychotic	0.029 (-0.018, 0.076)

Note. 95% confidence intervals in parentheses. Betas significant at p < .05 are bolded. 0 = not SGA; 1 = SGA.

eTable 8. Standardized General and Specific Factors Regressed on Birth Weight Coded in Kilograms Controlling Gestational Age Based on Siblings Born Within 2.51, 3, 4, 6, 7, 8, 9, and 10 Years Apart

	Factors				
Years apart	General factor	Specific anxiety factor	Specific externalizing factor	Specific neurodevelopmental factor	Specific psychotic factor
<2.51	-.027 (.017); **.045** (.012)	-.079 (.041); -.040 (.027)	.040 (.022); -.051 (.015)	**-.150** (.022); **.051** (.015)	.005 (.050); .027 (.034)
<3	**-0.030** (.015); **.041** (.010)	-.069 (.036); -.036 (.024)	.037 (.020); **-.050** (.014)	**-.163** (.019); **.043** (.013)	.030 (.043); .032 (.286)
<4	**-0.040** (.013); **.035** (.009)	-.057 (.030); -.021 (.020)	.030 (.017); **-.044** (.012)	**-.163** (.017); **.053** (.011)	.017 (.036); .012 (.025)
<6	**-.048** (.012); **.033** (.008)	-.021 (.029); -.020 (.019)	**.051** (.016); **-.045** (.011)	**-.136** (.016); **.044** (.011)	.019 (.035); -.006 (.024)
<7	**-.049** (.012); **.033** (.008)	-.042 (.029); -.017 (.019)	**.048** (.016); **-.042** (.011)	**-.144** (.016); **.050** (.011)	.014 (.034); -.006 (.023)
<8	**-.050** (.012); **.033** (.008)	-.030 (.029); -.023 (.019)	**.053** (.016); **-.044** (.011)	**-.148** (.016); **.048** (.011)	.014 (.034); -.009 (.023)
<9	**-.047** (.012); **.031** (.008)	-.016 (.029); -.017 (.018)	**.055** (.016); **-.041** (.011)	**-.141** (.016); **.047** (.011)	.031 (.034); -.009 (.023)
<10	**-.048** (.012); **.034** (.008)	-.038 (.028); -.027 (.018)	**.049 (.016);** **-.043 (.011)**	**-.150** (.016); **.048** (.010)	.016 (.034); -.010 (.023)

Note. The first beta corresponds to a linear change in birth weight, and the second beta corresponds to a squared change in birth weight. Standard errors are presented in parentheses. Betas significant at $p < .05$ are bolded.

eTable 9. Standardized General and Specific Factors Regressed on Birth Weight Coded in Kilograms Controlling Gestational Age Based on Sex-Concordant Sibling Pairs Only

	Fixed effect among male-concordant sibling pairs			Fixed effect among female-concordant sibling pairs	
Factor	Birth weight beta	Birth weight^2 beta		Birth weight beta	Birth weight^2 beta
General	**-0.059** (-0.108, -0.010)	0.014 (-0.019, 0.047)		**-0.083** (-0.130, -0.036)	0.025 (-0.012, 0.062)
Specific anxiety	-0.100 (-0.210, 0.010)	0.009 (-0.065, 0.083)		0.033 (-0.077, 0.143)	0.022 (-0.060, 0.104)
Specific externalizing	0.054 (-0.009, 0.117)	-0.016 (-0.059, 0.027)		0.073 (-0.003, 0.149)	-0.018 (-0.075, 0.039)
Specific neurodevelopmental	**-0.107** (-0.168, -0.046)	**0.088** (0.049, 0.127)		**-0.116** (-0.190, -0.042)	**0.080** (0.023, 0.137)
Specific psychotic	0.089 (-0.040, 0.218)	-0.059 (-0.147, 0.029)		-0.109 (-0.264, 0.046)	0.002 (-0.129, 0.133)

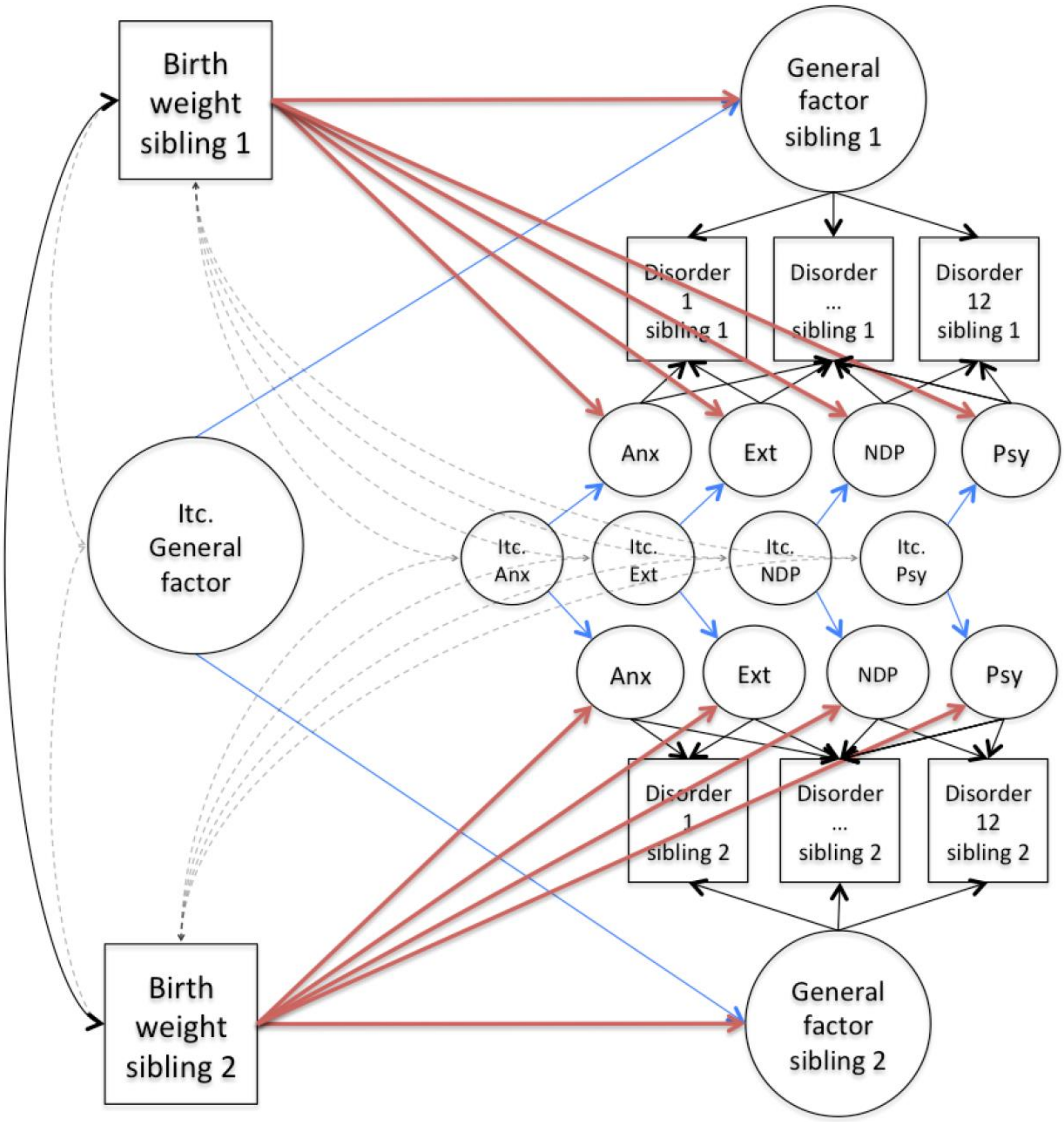
Note. 95% confidence intervals in parentheses. Betas significant at $p < .05$ are bolded.

eTable 10. Standardized General and Specific Factors Regressed on Birth Weight Coded in Kilograms Controlling Gestational Age Among Those Born Within Three Standard Deviations of the Mean of Birth Weight and Gestational Age

	Fixed effect	
Factor	Birth weight beta	Birth weight^2 beta
General	**-0.046** (-0.070, -0.022)	0.016 (-0.009, 0.041)
Specific anxiety	-0.058 (-0.117, 0.001)	-0.029 (-0.088, 0.030)
Specific externalizing	0.026 (-0.007, 0.059)	**-0.051** (-0.084, -0.018)
Specific neurodevelopmental	**-0.139** (-0.172, -0.106)	**0.065** (0.032, 0.098)
Specific psychotic	-0.002 (-0.071, 0.067)	**-0.077** (-0.146, -0.008)

Note. 95% confidence intervals in parentheses. Betas significant at $p < .05$ are bolded. Three standard deviations from the mean of birth weight corresponded to a birth weight between 1.94 and 5.12 kilograms. Three standard deviations from the mean of gestational age corresponded to a being born between 34.41 and 44.75 weeks.

eFigure 1. Latent Exploratory Factors Regressed on Birth Weight and Covariates (Not Shown)



Absence of dashed lines indicate random effects model. Presence of dashed lines indicate fixed effects model. Blue lines were fixed at unity. Itc = Random sibling pair intercept; Anx = Specific anxiety factor; Ext = Specific externalizing factor; NDP = Specific neurodevelopmental factor; Psy = Specific psychotic factor. See Table 2 for factor loadings.

eFigure 2. Scree Plot of Adverse Outcomes