

Prediction From Low Birth Weight to Female Adolescent Depression

A Test of Competing Hypotheses

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Context: Low birth weight (LBW) predicts later-onset hypertension and diabetes mellitus. Its role as a predictor of depression is unclear.

Objectives: To examine whether LBW predicts depression in male and female children and adolescents and to compare the following 2 hypotheses: Low birth weight is one among several perinatal, childhood, and adolescent risk factors for depression (biopsychosocial hypothesis). Low birth weight is a marker for poor intrauterine conditions that provoke adjustments in fetal development, with long-term consequences for stress response (fetal programming hypothesis).

Design: A representative population-based sample from an 11-county area in western North Carolina was assessed annually for psychiatric disorders between the ages of 9 and 16 years. We tested the prediction from LBW and depression in models that included LBW only, LBW plus other prenatal and perinatal adversities, LBW plus significant perinatal and childhood adversities, and LBW plus significant perinatal and childhood adversities and adolescent correlates.

Setting: Academic research.

Participants: There were 1420 participants, of whom 49% were female.

Main Outcome Measure: Cumulative prevalence of DSM-IV depressive disorder at 1 assessment or more during childhood (age range, 9-12 years) and during adolescence (age range, 13-16 years).

Results: The cumulative prevalence of depression among adolescent girls with LBW was 38.1% (95% confidence interval [CI], 16.3%-66.0%) compared with 8.4% (95% CI, 5.2%-13.3%) among adolescent girls with normal birth weight. Rates among children and adolescent boys did not exceed 4.9%. In adolescence, there was a significant interaction between LBW and sex (odds ratio, 0.2 [95% CI, 0.1-0.5]; $P < .001$). Low birth weight predicted female adolescent depression after controlling for other perinatal, childhood, and adolescent adversities. Girls with LBW and normal birth weight with no adversities had no adolescent depression, but each additional adversity increased the risk of in girls with LBW more than in girls with normal birth weight. Low birth weight did not predict other psychiatric disorders in either sex.

Conclusions: Low birth weight predicts depression in adolescent girls but not boys. Data support fetal programming over the biopsychosocial hypothesis, suggesting vulnerability to adversities in girls with LBW after puberty.

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FINDINGS FROM STUDIES THAT link low birth weight (LBW) with adolescent¹ and adult² depression raise the possibility that depression might follow a developmental pattern seen in other adult-onset chronic diseases such as cardiovascular disease and type 2 diabetes mellitus. That is, suboptimal fetal development (herein indexed by LBW) might increase later illness liability, particularly under stressful conditions.^{3,4}

On the question of whether LBW predicts depression, the evidence is conflicting. Some studies^{1,2,5-12} have shown an effect of LBW on later depression, while other studies¹³⁻²⁰ have not. Such uncer-

tainty could be caused by lack of specificity about effects of birth weight on depression in different age-by-sex groups. In childhood, rates of depression are equally low in both sexes. At about age 13 years, prevalence rises markedly among girls but not among boys.^{21,22} Any explanation of a link between LBW and depression needs to consider these sex-by-age differences.

In this study, we tested 2 hypotheses about possible causal links between fetal development and later illness. One hypothesis treats LBW simply as 1 of a range of risk factors, such as genetic predisposition, childhood and adolescent adversities, and maternal stress in the prenatal and perinatal period, in which accumulation

over time predicts later psychopathology.²³ We refer to this as the *biopsychosocial hypothesis*, according to which LBW adds 1 more to the list of adversities that increase risk for depression. The second explanation, the *fetal origins hypothesis*,²⁴ sometimes called the *Barker hypothesis*,⁴ posits that LBW is a marker for poor intrauterine conditions for growth and development. These provoke adjustments in fetal physiologic development, with long-term consequences for function and health.²⁵ According to this model, there is “a mismatch between physiologic capacities established in early development and the environments in which they later must function.”^{4(p98)} Adjustments by the fetus to suboptimal conditions may maximize chances for survival during gestation and early development but at a deferred cost if such adjustments leave the individual less well prepared to deal with conditions encountered later in life. In this case, effects of LBW might be latent until the system encounters adversities that strain its capacity to adapt. The stress threshold may be lower than that which would trigger illness in individuals of normal birth weight (NBW). For example, firm evidence links suboptimal fetal development with increased liability to conditions in adulthood (altered glucose tolerance, raised blood pressure, and hypertension) that are precursors of diabetes mellitus and cardiovascular disease, particularly under stressful conditions.^{2-5,24,26,27} If the fetal origins hypothesis pertains to depression, we would predict that the effect of at least some of the adversities known to increase risk for depression would be increased in individuals with LBW.

Low birth weight has been implicated in risk for several other psychiatric disorders, including schizophrenia,^{28,29} attention-deficit/hyperactivity disorder (ADHD),^{9,10,16,17,30} and eating disorders.³¹ Research in these areas has not so far tested a fetal origins hypothesis against alternatives, to our knowledge. However, it may be that intrauterine growth retardation creates risk for a range of psychiatric outcomes at different developmental stages corresponding to times of specific risk to the developing organism.³² There is a considerable amount of evidence that boys are more susceptible to early developmental insults and, as a result, show higher rates of early-onset neurodevelopmental problems such as autism and ADHD.³³ Girls, on the other hand, seem more likely to experience later-onset disorders such as depression³³ that may be linked with social, psychological, or hormonal challenges of puberty.³⁴

In this article, we use data from a longitudinal population-based sample of children and adolescents to examine risk from LBW to depression and other disorders. We examine the role of comorbidity and compare the biopsychosocial and fetal origins hypotheses.

METHODS

STUDY PARTICIPANTS

Data are from the Great Smoky Mountains Study, a longitudinal study of the development of psychiatric disorders and the need for mental health services among rural and urban youth.³⁵⁻³⁷ A representative sample of 3 cohorts of children aged 9, 11, and 13 years at intake in 1993 was recruited from 11 counties in

western North Carolina. Potential participants were selected from among the population of some 20 000 children using a household equal probability, accelerated cohorts design.³⁸ The accelerated cohorts design means that during several years of data collection each cohort reaches a given age in a different year, thus controlling for cohort effects.³⁹ For example, the 3 cohorts in 1996 were aged 12, 14, and 16 years; conversely, the 3 cohorts were aged 16 years in 1996, 1998, and 2000.

Youth with behavior problems were oversampled by means of a screening questionnaire administered to a parent (usually the mother) of the first-stage sample (n=3896). The screen consisted mainly of the externalizing (behavioral) problems scale of the Child Behavior Checklist⁴⁰ and was administered by telephone or in person. Most families (95%) contacted completed the screen. All children scoring above a predetermined cutoff point (the top 25% of the total scores), plus a 1-in-10 random sample of the rest (ie, the remaining 75% of the total scores) were recruited for detailed interviews. Of those recruited, 80% (n=1070) agreed to participate, of whom 49% were girls.

About 8% of the area residents and the sample are African American, and less than 1% are Hispanic. American Indians make up only about 3% of the population of the study area but were oversampled from school records using the same screening procedure but recruiting everyone irrespective of screen score. Of 456 American Indian children identified, screens were obtained on 96%, and 350 participated in the study. The total study sample comprised 1420 participants.

Data for each participant were weighted in inverse proportion to his or her probability of selection. The weights are incorporated into the data analyses so that the results presented herein are representative of the population from which the sample was drawn, not of their distribution in the sample.

Data used in these analyses are from 1993 to 2000, when the participants were aged 9 to 16 years. Response rates ranged from 74% to 94% a year, with a mean of 83%.

INTERVIEW PROTOCOL

Psychiatric and Psychosocial Measures

Psychiatric diagnoses and most psychosocial adversities were assessed using the Child and Adolescent Psychiatric Assessment (CAPA), an interviewer-based diagnostic interview.⁴¹ A detailed glossary provides the operational rules for identifying clinically significant symptoms. Scoring programs for the CAPA, written in SAS software (SAS Institute, Cary, NC), combined information about the date of onset, duration, and intensity of each symptom to create diagnoses according to the DSM-IV.⁴² For this study, depression was defined as major depression, dysthymic disorder, or depression not otherwise specified. The time frame of the CAPA is the 3 months before the interview. The 2-week test-retest reliability of the CAPA diagnoses in children aged 10 to 18 years is comparable to that of other structured child psychiatric interviews.^{36,41} Exact definitions of the adversities listed in **Table 1** and **Table 2** are available from the author.

Prenatal and perinatal information was obtained from the mothers. We defined LBW as 2500 g or less (≤ 5.5 lb) in conformity with most of the literature.⁴³ Mothers retrospectively rated the length of gestation and pregnancy and any birth difficulties on scales of 0 to 5. Other indexes of perinatal adversity were having a mother younger than 18 years at the birth of the child and having a mother or father who left school before the 11th grade. Subjects' weight and height growing up were measured at each interview (ie, from ages 9-13 years onward) and were used to calculate the body mass index. Obesity was defined using the Centers for Disease Control and Prevention guidelines (<http://apps.nccd.cdc.gov/dnpabmi/calculator>

Table 1. Prenatal and Perinatal Effects on Female Adolescent Depression*

Prenatal and Perinatal Risk Factor	Prevalence of Risk Factor, %	Prevalence of Risk Factor With and Without Associated Depression, %		Odds Ratio (95% Confidence Interval) of Main Effect on Depression	P Value
		With	Without		
Low birth weight	5.5	3.6	22.3	5.0 (1.9-13.1)	.001
Mother <18 y	8.3	5.7	22.8	4.2 (1.1-10.9)	.003
Parent having <11th grade education	8.3	9.0	6.1
Difficult pregnancy	13.6	13.5	15.4
Difficult birth	8.6	9.1	6.7
Birth "very early"	9.9	6.8	19.8	3.4 (0.9-12.6)	.07

*Ellipses indicate variables dropped from the model because of nonsignificance.

.aspx). Lifetime parental psychiatric history was obtained from interviews with the parents of study subjects using the Composite International Diagnostic Interview.⁴⁴ Current maternal depression was assessed at each interview using the 13-item version of the Mood and Feelings Questionnaire.⁴⁵⁻⁴⁷ Information on parents' criminal history was obtained from the North Carolina criminal records database.

Procedures

Participants were interviewed as near as possible to their birthday each year. The study received ethical approval annually from Duke University, Emory University, and the Tribal Council of the Eastern Band of the Cherokee. Before each interview began, the parent and the child signed informed consent forms. Each parent and child was paid a small sum after the interview.

DATA MANAGEMENT AND ANALYSIS

For most analyses, we collapsed the data into the following 3 periods: perinatal period (pregnancy and birth), childhood (age range, 9-12 years), and adolescence (age range, 13-16 years), which was the latest age at which both the parent and child were interviewed. Adolescent depression was counted as present if it was diagnosed at 1 interview or more between the ages of 13 and 16 years. Similarly, childhood risk factors were defined as present if they were reported on 1 or more occasions in childhood, and adolescent risk factors or correlates were defined as present if they were reported on 1 occasion or more between the ages of 13 and 16 years. This means that data on perinatal risk (collected retrospectively) and adolescent risk were available for all subjects, but data on childhood risk were available for only 2 age cohorts (aged 9 and 11 years at intake), not for the oldest cohort (aged 13 years at intake).

Statistical tests were performed using generalized estimating equations in the SAS software version 6 (SAS Institute)⁴⁸ program GENMOD, which makes use of all available data for each analysis. We used the robust variance estimates (ie, sandwich-type estimates) together with sampling weights to adjust the standard errors of the parameter estimates to account for the 2-phase sampling design.⁴⁹

We first tested the predictive power of a range of perinatal factors, alone and in interaction with LBW. Next, we added childhood factors previously found to be associated with childhood psychopathology, including comorbid psychiatric disorders (<http://apps1.jhsph.edu/weaton.MDRF/main.pdf>). Those found to be significant in bivariate analyses were combined in a model that included the significant predictors from the first model and all the interactions with LBW. The third model added a similar set of factors measured during adolescence. In the fourth model, all significant predictors and cor-

relates from the 3 stages and all interactions with LBW were included simultaneously. We found no significant interactions; therefore, these were dropped from the analysis. We conducted a stepwise analysis removing variables 1 at a time until there was no further improvement in the Bayesian information criterion. Rejected variables were then reentered to guard against effects of collinearity.

RESULTS

Our results indicate that the cumulative prevalence of depression among adolescent girls with LBW was 38.1% (95% confidence interval [CI], 16.3%-66.0%) compared with 8.4% (95% CI, 5.2%-13.3%) among adolescent girls with normal birth weight. Rates among children and adolescent boys did not exceed 4.9%. In adolescence, there was a significant interaction between LBW and sex (odds ratio, 0.2 [95% CI, 0.1-0.5]; $P < .001$).

LBW AND DEPRESSION

As expected from national surveys,⁵⁰ more boys than girls were at or below 2500 g at birth (8.7% vs 5.7%). The odds ratio was 1.3 (95% CI, 0.9-1.8, $P = .22$).

Figure 1 shows the 3-month prevalence of depressive disorders at the ages of 9 to 16 years for boys and girls with LBW and NBW. The mean 3-month prevalence of depression among both sexes was low during childhood (0.9% [95% CI, 0.6%-1.5%]) and remained low in adolescent boys whether of LBW (0.20% [95% CI, 0.04%-1.90%]) or NBW (2.0% [95% CI, 1.1%-3.7%]). On average, 23.5% (95% CI, 9.0%-48.9%) of adolescent girls with LBW were depressed each year compared with 3.4% (95% CI, 2.0%-5.6%) of adolescent girls with NBW. Thirty-eight percent of adolescent girls with LBW had 1 depressive episode or more between the ages of 13 and 16 years. In a logistic regression analysis predicting adolescent depression from sex, LBW, and their interaction, LBW predicted a significant increase in risk for adolescent depression in girls but not in boys (interaction OR, 0.015 [95% CI, 0.001-0.172]; $P < .001$).

We tested the sensitivity of these findings to the definition of LBW as 2500 g or less by examining the prevalence of adolescent depression among girls at each 500 g of difference in birth weight. Birth weight above 2500 g showed no effect, and risk was equally high at all lower weights (details available from the author). Because LBW

Table 2. Childhood and Adolescent Effects on Female Adolescent Depression*

Risk Factor Present During ≥1 y	During Childhood†					During Adolescence‡				
	Prevalence of Risk Factor, %	Prevalence of Risk Factor With and Without Associated Depression, %		OR (95% CI)	P Value	Prevalence of Risk Factor, %	Prevalence of Risk Factor With and Without Associated Depression, %		OR (95% CI)	P Value
		With	Without				With	Without		
Family below federal poverty line	19.3	18.5	28.3	21.8	21.3	27.3
Parent unemployed	17.9	18.3	12.5	15.2	15.3	13.9
≥4 Children in home	3.2	3.4	0.0	7.6	8.1	2.2
Stepparent	11.1	11.0	11.6	18.0	18.2	15.7
Single parent	16.0	16.2	13.8	31.3	28.7	59.3	3.7 (1.5-9.2)	.004
Time in foster care	2.3	2.5	0.3	3.0	2.2	17.0	9.0 (2.3-35.3)	.002
Moved ≥4 times in 5 y	14.1	13.2	23.3	11.1	9.6	28.7	3.9 (1.3-11.0)	.01
Dangerous neighborhood	0.7	0.6	1.2	1.5	0.9	7.5
Dangerous school	0.1	0.1	0.0	3.6	3.3	7.3
Poor health	1.7	1.8	0.0	1.5	0.9	8.6	20.9 (3.2-137.7)	.002
Obesity	18.3	18.5	16.5	32.8	32.9	32.4
Lax parental supervision	5.5	5.8	2.9	18.1	16.3	38.1
Harsh parental discipline	4.4	4.6	1.9	2.4	1.5	11.6	9.3 (2.7-32.2)	<.001
Overprotective or intrusive parenting	1.5	1.7	0.0	8.3	7.7	49.0
Child treated as scapegoat	1.5	1.6	0.0	1.5	0.8	8.9	23.7 (4.9-114.8)	<.001
Violence between parents	13.8	13.0	21.5	11.5	10.8	19.0
Deviant peers	11.1	10.4	18.9	15.6	13.8	36.8	3.6 (1.4-9.3)	.006
Family structure change	8.6	8.5	9.2	10.5	9.7	18.3
Parental drug abuse	10.6	10.7	10.0	14.0	13.1	24.1
Parental crime	18.0	18.5	12.3	11.3	10.9	15.6
Parental mental illness	21.8	20.4	36.8	2.3 (0.9-5.7)	.09	25.4	21.9	64.0	6.3 (2.5-15.9)	<.001
Maternal depression	8.4	8.2	11.2	9.9	8.1	29.5	4.7 (1.7-13.2)	.003
Physical abuse	3.4	3.3	3.8	5.0	3.1	25.7	10.5 (3.2-36.3)	<.001
Sexual abuse	9.5	8.5	19.7	2.6 (0.9-8.1)	.09	6.5	5.5	17.3	3.6 (1.2-10.7)	.02
Neglect	1.4	1.3	2.4	5.4	3.0	32.1	15.4 (5.2-45.8)	<.001
Extreme stressor	39.1	36.9	63.7	3.0 (1.2-7.5)	.02	51.9	50.0	71.9	2.9 (1.1-7.8)	.04
Other life event	36.3	33.6	66.1	3.8 (1.5-9.5)	.004	56.0	52.7	91.8	10.1 (2.4-43.7)	.002
Anxiety disorders	4.2	3.8	8.6	7.2	3.8	44.6	20.2 (6.9-59.3)	<.001
Disruptive behavior disorders	3.5	2.7	12.5	5.2 (1.5-10.9)	.001	8.0	4.3	49.1	21.5 (7.9-58.2)	<.001
Posttraumatic stress disorder	13.2	12.1	25.0	14.1 (2.4-83.7)	.004	16.0	13.7	41.6	13.7 (3.4-55.1)	<.001
Drug abuse or dependence	NA	NA	NA	8.1	6.5	26.0	5.0 (1.6-15.4)	.005
School dropout	NA	NA	NA	1.8	1.1	8.4
Expulsion	NA	NA	NA	1.2	0.5	9.4	22.7 (4.1-125.7)	<.001
Criminal conviction	NA	NA	NA	2.6	2.3	6.1

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.
 *Ellipses indicate variables dropped from the model because of nonsignificance.
 †Age range, 9 to 12 years.
 ‡Age range, 13 to 16 years.

did not predict depression in boys, the remainder of the analyses focus on girls.

RISK IN INFANCY, CHILDHOOD, AND ADOLESCENCE

Table 1 summarizes results of bivariate analyses of birth weight, birth difficulties, length of gestation, pregnancy difficulties, and adverse perinatal environment as pre-

dictors of female adolescent depression. In addition to LBW, length of gestation and teen mother were predictive. In a multivariate model that included interaction terms only, LBW (OR, 9.4 [95% CI, 2.7-32.2]; *P*<.001) and teen mother (OR, 4.6 [95% CI, 1.6-13.2]; *P*=.005) significantly predicted adolescent depression; length of gestation dropped out of the model (OR, 1.1 [95% CI, 0.3-3.9]; *P*=.92). None of the interaction terms were significant.

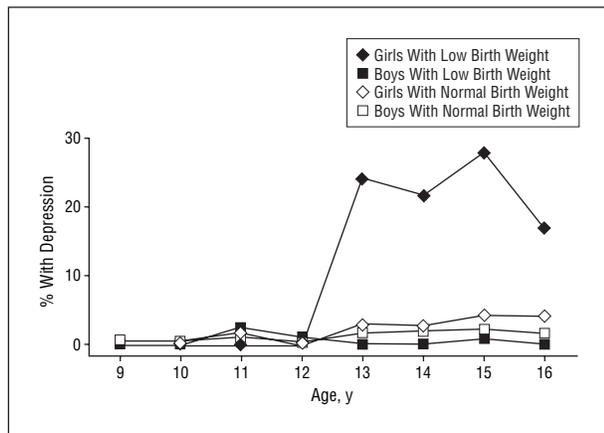


Figure 1. Three-month prevalence of depressive disorder by sex and birth weight.

The first 5 columns of Table 2 summarize the results of bivariate analyses of association between childhood (age range, 9-12 years) adversities and adolescent depression. Sexual abuse, parental mental illness, unstable family structure, disruptive behavior disorders, and other traumatic or nontraumatic life events were predictive. In a multivariate model that included LBW and teen mother from the previous model, these 2 variables remained significant (LBW OR, 7.6 [95% CI, 2.7-20.9]; $P < .001$; and teen mother OR, 3.6 [95% CI, 1.4-9.6]; $P = .01$). The only childhood predictor to remain in the model was nontraumatic life events (OR, 4.5 [95% CI, 1.7-12.1]; $P = .003$). None of the interactions with LBW were significant.

As summarized in the last 5 columns of Table 2, many factors were significantly associated with depression in bivariate analyses of adolescent correlates. In the multivariate model that included the significant perinatal and childhood predictors, teen mother and nontraumatic life events dropped out of the model. Low birth weight continued to predict depression (OR, 7.3 [95% CI, 2.0-26.7]; $P = .003$). Significant correlates were harsh parental discipline (OR, 5.7 [95% CI, 1.3-25.0]; $P = .02$) and nontraumatic life events (OR, 5.7 [95% CI, 1.6-20.8]; $P = .008$). Adolescent depression was comorbid with anxiety disorders (OR, 15.5 [95% CI, 5.1-47.7]; $P < .001$), disruptive behavior disorders (OR, 11.2 [95% CI, 3.8-33.1]; $P < .001$), and posttraumatic stress disorder (OR, 11.3 [95% CI, 2.3-54.9]; $P = .003$). None of the interaction terms were significant.

Therefore, in the first comparison between hypotheses, LBW did not perform like other more distal markers of adversity that disappeared from the model as more proximal measures were added. Instead, it stayed in the model through adolescence.

We next compared the 2 hypotheses about the role of LBW in female adolescent depression by adding all the significant adversities to create a scale score. If LBW were simply 1 more risk factor, depression in girls with LBW should increase in parallel with depression in girls with NBW. Under the fetal programming hypothesis, LBW should have little effect in the absence of other stressors except to act as a potentiator of the effect of other adversities.

Figure 2 shows the prevalence of adolescent depression among girls with LBW and NBW at different levels of adversity. A girl who experienced no other risk factors

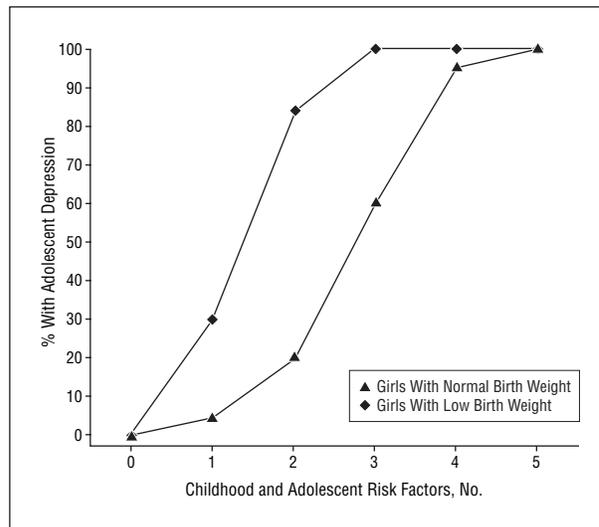


Figure 2. Risk of adolescent depression in girls of normal birth weight and low birth weight by number of childhood and adolescent risk factors predicting depression.

except LBW was at no increased risk for adolescent depression: none of the girls with LBW or NBW without adversities were depressed between the ages of 13 and 16 years. However, in the presence of a single adversity, depression in girls with LBW increased to 19.5% compared with 3.6% in girls with NBW. Adding another risk factor increased the LBW risk to 68.5% compared with 19.7%. Ninety-one percent of girls with LBW with 3 risk factors and 100% of girls with LBW with 4 risk factors experienced adolescent depression compared with 76.4% and 85.0%, respectively, of girls with NBW. Therefore, rates of depression increased much more rapidly with increasing risk in girls with LBW, but there was little effect of birth weight at the lowest and highest risk levels. These findings are more consistent with the fetal programming hypothesis than with the biopsychosocial hypothesis.

We repeated the analyses including only girls with diagnoses of major depressive disorder and dysthymia. The results were essentially unchanged.

LBW AND OTHER PSYCHIATRIC DISORDERS

We examined the effect of LBW on child and adolescent anxiety disorders, symptoms of posttraumatic stress disorder (because the full diagnosis was rare), disruptive behavior disorders (conduct disorder, oppositional defiant disorder, and ADHD), and abuse of or dependence on alcohol, marijuana, and other drugs of abuse. Full details are available from the author. Only the following 3 disorders showed any effect of LBW: social phobia, posttraumatic stress symptoms, and generalized anxiety disorder. In adolescence, all were 3 times more common in girls with LBW than in boys or in girls with NBW, although the differences were not significant using generalized estimating equations. When combined into a single variable, the effect was significant (OR, 4.7 [95% CI, 1.2-18.2]; $P = .02$). However, all of these conditions are comorbid with depression. When depression was included in the model, the effect of the anxiety disorders

disappeared (depression OR, 5.4 [95% CI, 2.0-14.5]; $P < .001$; and anxiety OR, 1.7 [95% CI, 0.6-4.5]; $P = .31$). Among the girls with LBW, only 1 had an anxiety disorder without depression. In summary, the effect of LBW was specific to depression; the association with adolescent social phobia, posttraumatic stress disorder, and generalized anxiety disorder seemed to be the result of comorbidity between these conditions and depression.

COMMENT

Although only 5.7% of the girls in the Great Smoky Mountains Study sample were of LBW, 38.1% of these girls experienced 1 or more depressive episodes between the ages of 13 and 16 years. The population attributable risk³¹ for adolescent depression associated with LBW in girls was 18% (ie, if no girls were to be born with birth weights of ≤ 2500 g, 18% fewer adolescent girls would have depressive episodes).

Since 1990, studies have been published supporting and refuting the idea that LBW predicts depression. The accumulation of evidence has not yielded a consensus. Articles published since 2000 (3 studies⁵⁻⁷ for and 3 studies^{13,14,19} against the theory) are as divided as those published earlier (4 studies⁸⁻¹¹ for and 2 studies^{16,18} against theory).

We examined whether a focus on female adolescent depression could clarify the issue. Most studies of LBW and depression have not reported the separate sex-by-age analyses needed to test whether LBW contributed specifically to adolescent female depression. Of the 2 studies^{7,8} that did so, both found that LBW was a much stronger risk factor for female than male adolescent depression. However, they did not compare children with adolescents, nor did they offer any explanations. We extend these findings by pitting the 2 explanatory hypotheses of accumulated biopsychosocial risk vs fetal programming against each other.

The evidence from these analyses argues in favor of the fetal programming hypothesis. First, if LBW were merely 1 of a cluster of generic risk factors for psychopathology it should predict other disorders as well as depression and do so throughout late childhood and adolescence in boys and in girls. In fact, LBW predicted only depression, only in adolescence, and only in girls. Second, LBW did not act like just 1 more risk factor. When no other adversities were present, the rate of female adolescent depression was 0% in girls with NBW and LBW. Yet, 20% of girls with LBW exposed to a single adversity had an episode of adolescent depression compared with 4% of girls with NBW, and the difference among girls with 2 adversities was even more marked (68% vs 20%). Low birth weight acted more like a potentiator of other risk factors than a separate adversity.

Low birth weight has been implicated in risk for schizophrenia,^{28,29} ADHD,^{9,10,16,17,30} and eating disorders.³¹ Too few Great Smoky Mountains Study participants had schizophrenia or eating disorders to test for effects of LBW. No effects on ADHD were found, but this may be because data collection did not begin until the ages of 9 to 13 years, past the peak age at onset of ADHD. Studies of other psychiatric disorders have not yet tested a fetal ori-

gins hypothesis against alternatives, to our knowledge. The possibility remains that intrauterine growth retardation creates risk for a range of psychiatric outcomes at different developmental stages depending on the timing of exposure in relation to time-specific vulnerabilities of the developing organism.³²

The chief weakness of the design for the purpose of these analyses is retrospective recall by mothers of the study subjects' birth weight, as well as the simple scales ranging from 0 to 5 that were used to record gestational age and other perinatal information. For participants, the study began at age 9 years, and with the 1420 subjects spread across an 11-county area, we lacked the resources to track down birth records. However, a recent analysis comparing medical records with maternal recall some 30 years later found maternal recall to be accurate for birth weight (intraclass correlation coefficient, 0.76), although less so for gestational age (intraclass correlation coefficient, 0.64).⁵² Our study also lacked measures of maternal psychopathology or drug use during pregnancy. Therefore, it could not examine the relationship between the causes of LBW³³⁻⁵⁵ and later depression but only its consequences. Other shortcomings include lack of data on the oldest cohort at the ages of 9 to 12 years, because they entered the study at age 13 years, as well as small numbers for some tests of interactions. Also, the annual interviews focused on a 3-month window, so it is possible that episodes of depression developed and disappeared in the 9 months between interviews. However, there is no apparent reason why this should happen to a different extent in subjects with LBW vs NBW. Strengths of this study include a representative population sample and data on psychiatric disorders based on structured interviewer-based psychiatric assessments at close intervals throughout later childhood and adolescence.

The findings need replication in larger samples that include prospective data from birth to adulthood. Important next steps will include separate examination of the many different hormonal, morphological, psychological, and social aspects of puberty that might best explain the increase in risk seen in adolescence, herein indexed by age. In previous work, it was demonstrated that rising pubertal levels of the hormones estradiol and testosterone increase the risk of depression in girls independently of body morphologic structure, the timing of pubertal changes, or stress levels.⁵⁶ The fetal origins hypothesis also directs attention to intergenerational transmission of risk, because maternal risk behaviors such as drinking and smoking during pregnancy could affect birth weight and postnatal rearing environment.⁵⁷ The present study lacked power to examine these patterns separately in girls with LBW, but such a study could yield clues to the mechanisms linking intrauterine stress and adolescent depression. For the present, the findings suggest that pediatricians and parents of girls who were of LBW should pay close attention to their mental health as they enter puberty.

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