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ONLINE FIRST

Preterm Birth and Psychiatric Disorders in Young Adult Life

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Context: Preterm birth, intrauterine growth restriction, and delivery-related hypoxia have been associated with schizophrenia. It is unclear whether these associations pertain to other adult-onset psychiatric disorders and whether these perinatal events are independent.

Objective: To investigate the relationships among gestational age, nonoptimal fetal growth, Apgar score, and various psychiatric disorders in young adult life.

Design: Historical population-based cohort study.

Setting: Identification of adult-onset psychiatric admissions using data from the National Board of Health and Welfare, Stockholm, Sweden.

Participants: All live-born individuals registered in the nationwide Swedish Medical Birth Register between 1973 and 1985 and living in Sweden at age 16 years by December 2002 (n=1 301 522).

Main Outcome Measures: Psychiatric hospitalization with nonaffective psychosis, bipolar affective disorder, depressive disorder, eating disorder, drug dependency, or alcohol dependency, diagnosed according to the *International Classification of Diseases* codes for 8

through 10. Cox proportional hazards regression models were used to estimate hazard ratios and 95% CIs.

Results: Preterm birth was significantly associated with increased risk of psychiatric hospitalization in adulthood (defined as ≥ 16 years of age) in a monotonic manner across a range of psychiatric disorders. Compared with term births (37-41 weeks), those born at 32 to 36 weeks' gestation were 1.6 (95% CI, 1.1-2.3) times more likely to have nonaffective psychosis, 1.3 (95% CI, 1.1-1.7) times more likely to have depressive disorder, and 2.7 (95% CI, 1.6-4.5) times more likely to have bipolar affective disorder. Those born at less than 32 weeks' gestation were 2.5 (95% CI, 1.0-6.0) times more likely to have nonaffective psychosis, 2.9 (95% CI, 1.8-4.6) times more likely to have depressive disorder, and 7.4 (95% CI, 2.7-20.6) times more likely to have bipolar affective disorder.

Conclusions: The vulnerability for hospitalization with a range of psychiatric diagnoses may increase with younger gestational age. Similar associations were not observed for nonoptimal fetal growth and low Apgar score.

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ADVANCES IN PERINATAL care in the past 2 decades have led to improved survival of babies experiencing perinatal complications.¹ However, there is considerable evidence that such complications are associated with neurodevelopmental impairments²⁻⁴ and psychiatric morbidity later in life.^{5,6} The most extensively studied complications in relation to psychiatric illness include very preterm birth, nonoptimal fetal growth including intrauterine growth restriction, and delivery-related hypoxia.⁷

Two important questions remain unanswered. First, what is the specificity of the association? Most studies to date have investigated the relationship between prena-

tal and perinatal complications and schizophrenia,⁸⁻¹¹ but few have examined the relationship with other adult-onset psychiatric diagnoses. Although a population-based study found a significant association between obstetric complications and addictive behaviors,¹² perinatal adversities were not found to represent risk factors for bipolar affective disorder.¹³ A second question is whether these adverse events are independent risk factors for psychiatric illness or reflect shared etiologic mechanisms. There is often overlap between these events; thus, most babies who are born with a low birth weight are born preterm, and many also experience varying degrees of intrauterine growth failure,¹⁴ which is often complicated by hypoxia.¹⁵ In the few studies that have examined these complications as risk

Table 1. ICD Codes Used to Define the 6 Psychiatric Diagnoses of Interest

Diagnosis	ICD-8 Codes	ICD-9 Codes	ICD-10 Codes
Nonaffective psychosis	295, 297.9, 298.0-3, 298.9, 299.9	295, 297J, 298A-E, 298I-J	F20, F21, F23.1-2, F25, F28, F29
Depressive disorder	300.4, 296.0, 296.2	296C-D, 300E, 311	F32, all codes except F32.3; F33, all codes except F33.3
Bipolar affective disorder	296.1, 296.3	296A-B, 296E-J	F31
Eating disorders	306.5	307B, 307F, 783A, 783G	F50
Drug dependency	304	304	F11-F19
Alcohol dependency	291.2-3, 291.9, 303	291, 303, 305	F10

Abbreviation: ICD, *International Classification of Diseases*.

factors for schizophrenia, the results are inconsistent. Some studies have found an increased risk in individuals who were born preterm but not in those with low birth weight¹⁶ and others in individuals with low birth weight or preterm birth but not in those who were small for gestational age,⁹ which is commonly used to define fetal growth restriction. Other researchers have reported smallness for gestational age as conferring the greatest risk,¹⁰ and still others have demonstrated a stronger effect for hypoxia compared with other adverse perinatal factors.⁸ Establishing the relationship among all 3 types of complications, not just in schizophrenia but in other severe mental disorders, would increase our understanding of the etiology of these disorders and the extent to which this is shared and may allow the most vulnerable individuals to be identified early in life.

This study used population-based data from Sweden to investigate associations among very preterm birth, non-optimal fetal growth, Apgar score, and risk of psychiatric hospitalization in young adulthood due to nonaffective psychosis, depressive disorder, bipolar affective disorder, eating disorder, alcohol dependency, and drug dependency. To our knowledge, this is the first study to investigate the effects of these 3 major pregnancy outcomes on such a broad range of adult psychiatric outcomes.

METHODS

DATA SOURCE

We used data from the National Board of Health and Welfare, Stockholm, Sweden, and Statistics Sweden, which provided individually linked data in 3 population-based registers, the Swedish Medical Birth Register, the Swedish National Hospital Discharge Register, and the Swedish Multi-Generation Register, by means of the unique personal 10-digit National Registration Number assigned to each resident of Sweden. The study was approved by the Karolinska Institutet ethics committees.

The Swedish Medical Birth Register contains prospectively collected information on more than 99% of all hospital births in Sweden since 1973. During pregnancy and delivery, information is prospectively collected and noted on standardized records, a copy of which is forwarded to the Birth Register after delivery. More than 95% of Swedish pregnant women attend antenatal clinics before the 15th gestational week,¹⁷ and information in the Birth Register includes prospectively collected data from the first antenatal visit up to the time when mother and child are discharged from the hospital.

The following pregnancy outcomes were selected for analysis: gestational age at birth, birth weight for gestational age, and Apgar score at 5 minutes. Gestational age was estimated from the date of the mother's last menstrual period and was stratified into very

preterm (<32 completed weeks), moderately preterm (32-36 weeks), term (37-41 weeks), and postterm (≥ 42 weeks). No data for estimated date of delivery by ultrasound was available in the Swedish Medical Birth Register during the time of the study (1973-1985); therefore, we did not calculate gestational age by ultrasound. Birth weight for gestational age was regarded as a measure of fetal growth and was measured as birth weight standard deviation scores, defined as differences between actual and fitted birth weight divided by fitted standard deviation of birth weight, for each gestational week according to the Swedish sex-specific birth weight curve.¹⁸ More than 2 SDs below the mean birth weight for gestational age was regarded as light for gestational age, thus an indication of non-optimal fetal growth; -2 to 2 SDs as appropriate weight for gestational age; and greater than 2 SDs as heavy for gestational age. Apgar score at 5 minutes was assessed by the presence of events such as being blue at birth, necessary resuscitation, neonatal cyanosis, and apnea.¹⁹ An Apgar score of 0 to 3 means that the infant is severely distressed; 4 to 6, the newborn is distressed; and 7 to 10, the infant is in fairly good or excellent condition. Apgar scores can reflect hypoxia, ischemia, sepsis, and hypovolemia, among others.

The following demographic and maternal characteristics were studied as covariates: sex, maternal age (stratified as <17, 17-19, 20-24, 25-29, 30-39, and ≥ 40 years), parity (1, 2-3, and ≥ 4 children), and level of formal full-time education after compulsory school in the Swedish educational system (0-2: ≥ 9 years of compulsory education plus up to 2 years of postcompulsory education [upper secondary school]; 3-4: 9 years of compulsory education plus 3-4 years of postcompulsory education; and "higher": 9 years of compulsory education plus >4 years of postcompulsory education). We did not include maternal smoking in the analyses as this variable was introduced in 1983 in the Swedish Medical Birth Registry and thus was available only for individuals born in 1983-1985.

The Swedish National Hospital Discharge Register is a compilation of each individual hospital's discharge records and provides data on hospital discharges and diagnoses, classified according to the World Health Organization *International Classification of Diseases, 8th Revision (ICD-8)* through 1986, *ICD-9* from 1987 through 1996, and *ICD-10* from 1997 through 2002. Discharge diagnoses are formulated by an attending physician and are based on observations made during hospitalization, evaluation of the service user, and medical records at discharge. The ICD discharge diagnoses used in Swedish registers have been found to be largely in agreement with diagnoses based on DSM criteria²⁰ and those based on semistructured interviews and medical records,²¹ with an overall positive predictive value of 85% to 95%.²² Computerized information is available from 1986 onward. Each episode of hospital care contains a unique personal identifier (a 10-digit National Registration Number), which we used to match individuals' diagnoses with information extracted from the Swedish Medical Birth Register and the Swedish Multi-Generation Register, described later herein. This allowed us to investigate selected psychiatric diagnoses in relation to neonatal and maternal sociodemo-

graphic factors and to account for the effects of maternal psychiatric family history.

Table 1 provides the ICD codes used to define the psychiatric outcome measures: nonaffective psychosis (including schizophrenia and schizoaffective disorder, which we acknowledge may not be regarded as being “nonaffective”), depressive disorder (which is, however, likely to overlap with bipolar affective disorder in the absence of frank mania), bipolar affective disorder (in the presence of frank mania), eating disorder, drug dependency, and alcohol dependency.

The Swedish Multi-Generation Register allows the identification of an “index person” and his or her first-degree relatives (parents, siblings, and offspring) as long as the parent was born after January 1, 1932, and was registered as a Swedish resident at any time after 1960.²³ We used the Multi-Generation Register to identify the maternal psychiatric family history (restricted to the participant’s mother) of all individuals in the defined study population. Diagnoses could have been made anytime during the lifetime of the participant’s mother (up to the time of death or December 2002), and the same spectrum of diagnoses was included as for the cohort members themselves. We did not study paternal psychiatric family history because, to our knowledge, there are no previous studies relating paternal psychiatric disorders to the risk of preterm birth in their offspring.

ANALYTIC COHORT

We identified all individuals registered in the Swedish Medical Birth Register between 1973 and 1985 who were alive and living in Sweden at age 16 years by December 2002 (n=1 301 522). Linkage analysis with the Hospital Discharge Register identified all individuals with a primary or secondary diagnosis of the following psychiatric disorders: nonaffective psychosis (n=669), depressive disorder (n=2333), bipolar affective disorder (n=217), eating disorder (n=997), drug dependence (n=2973), and alcohol dependence (n=3334). Individuals were censored at their first episode of one of the selected disorders. For example, individuals who (first) developed depressive disorder and thereafter nonaffective psychosis were not included in the analysis of nonaffective psychosis. Individuals who (first) developed a nonpsychiatric disorder (eg, cancer) and thereafter a selected psychiatric disorder (eg, nonaffective psychosis) were included in the analysis of nonaffective psychosis. The analyses included only first hospitalizations with a selected diagnosis after an individual’s 16th birthday, which excluded the possibility that participants had been previously hospitalized with any of the listed diagnoses.

STATISTICAL ANALYSIS

A historical population-based cohort design was used. Descriptive summaries of the data were calculated for the total cohort and in relation to unadjusted incidence rates per 10 000 person-years of hospitalization with the studied psychiatric diagnoses. The 95% CIs were calculated under the assumption of the Poisson distribution.

Cox proportional hazards regression models were used to examine the association between perinatal factors (gestational age, nonoptimal fetal growth, and Apgar score) and risk of individual psychiatric diagnoses. Hazard ratios and 95% CIs were computed. Individuals were censored at the occurrence of hospitalization with a diagnosis of interest, death, emigration, or the end of follow-up, which was December 2002.

In the analysis of crude associations, each exposure (gestational age, nonoptimal fetal growth, and Apgar score) was examined individually. The adjusted model included all these fac-

tors as well as sex, parity, mother’s age at delivery, mother’s educational level, and maternal psychiatric family history. This model allowed us to examine the independent and unique association of each factor and each psychiatric diagnosis. Data were analyzed using a commercially available software program (SAS, version 8 for UNIX; SAS Institute, Inc).

RESULTS

The mean (SD) age of the population enrolled for follow-up was 23.0 (4.1) years. The mean (SD) age at first hospitalization for all diagnoses was 20.9 (3.01) years and for individual diagnostic clusters was as follows: nonaffective psychosis, 21.7 (3.0) years; depressive disorder, 21.1 (3.1) years; bipolar affective disorder, 21.1 (3.1) years; eating disorder, 20.0 (2.9) years; drug dependency, 21.4 (2.8) years; and alcohol dependency, 20.6 (3.0) years.

Table 2 provides descriptive summaries of the data, including pregnancy outcomes (gestational age, birth weight for gestational age, and Apgar score at 5 minutes), sex, maternal age, maternal education, and maternal psychiatric family history, for the total cohort and in relation to unadjusted incidence rates per 10 000 person-years of hospitalization with the studied psychiatric diagnoses.

Table 3 presents crude and adjusted hazard ratios for psychiatric diagnosis in relation to gestational age, nonoptimal fetal growth, and Apgar score.

PRETERM BIRTH

In the crude models, preterm birth was significantly associated with increased risk of psychiatric hospitalization in a monotonic manner across a range of psychiatric disorders, including nonaffective psychosis, depressive disorder, and bipolar affective disorder. All the associations remained statistically significant after controlling for indicators of nonoptimal fetal growth, Apgar score, maternal characteristics, and sociodemographic variables. Compared with individuals born at 37 to 41 weeks (the reference group), those born at 32 to 36 weeks of gestation were 60% more likely to have nonaffective psychosis, 34% more likely to have depressive disorder, and more than 2 times as likely to have bipolar affective disorder. Those born at less than 32 weeks had a more than doubled risk of nonaffective psychosis, almost a tripled risk of depressive disorder, and a more than 7 times higher risk of bipolar affective disorder.

Compared with the reference group, very preterm birth (<32 weeks) was also associated with a more than 3-fold increased risk of eating disorders, and “moderate” preterm birth (32-36 weeks) was associated with an increased risk of drug and alcohol dependency in crude and adjusted models.

NONOPTIMAL FETAL GROWTH

In the crude models, “small for gestational age” (standard deviation score ≤ -2) was significantly associated with increased risk of psychiatric hospitalization with drug and alcohol dependency. These associations remained statistically significant after controlling for gestational age

Table 2. Distribution of Birth Characteristics and Potential Confounders in Individuals 16 Years and Older (N = 1301 522)

Variable	Total Sample, No. (%)	Nonaffective Psychosis (n = 669)	Depressive Disorder (n = 2333)	Bipolar Affective Disorder (n = 217)	Eating Disorder (n = 997)	Drug Dependency (n = 2973)	Alcohol Dependency (n = 3334)
		No./IR (95% CI) ^a	No./IR (95% CI) ^a	No./IR (95% CI) ^a	No./IR (95% CI) ^a	No./IR (95% CI) ^a	No./IR (95% CI) ^a
Gestational age, wk							
<32	5125 (0.4)	6/1.8 (0.7-4.0)	22/6.8 (4.2-10.2)	4/1.2 (0.3-3.1)	9/2.8 (1.3-5.3)	14/4.3 (2.3-7.2)	20/6.1 (3.8-9.5)
32-36	47 864 (3.7)	37/1.2 (0.8-1.6)	108/3.4 (2.8-4.1)	20/0.6 (0.4-1.0)	48/1.5 (1.1-2.0)	132/4.2 (3.5-5.0)	160/5.1 (4.3-5.9)
37-41	1 022 431 (78.6)	495/0.7 (0.6-0.8)	1720/2.5 (2.3-2.6)	153/0.2 (0.2-0.3)	746/1.1 (1.0-1.1)	2241/3.2 (3.1-3.3)	2475/3.5 (3.4-3.7)
≥42	221 022 (17.0)	126/0.7 (0.6-0.9)	471/2.8 (2.5-3.0)	40/0.2 (0.2-0.3)	191/1.1 (1.0-1.3)	571/3.3 (3.1-3.6)	657/3.8 (3.6-4.1)
Data missing	5080 (0.4)	5/1.2 (0.4-2.9)	12/3.0 (1.5-5.2)	0/0.0 (0.0-0.7)	3/0.7 (0.2-2.2)	15/3.7 (2.1-6.1)	22/5.4 (3.4-8.2)
Birth weight for gestational age, SDS							
<-2	43 334 (3.3)	26/0.8 (0.5-1.2)	102/3.1 (2.5-3.8)	10/0.3 (0.2-0.6)	32/1.0 (0.7-1.4)	51/4.8 (4.1-5.6)	156/4.8 (4.0-5.6)
-2 to 2	1 219 783 (93.7)	625/0.7 (0.7-0.8)	2178/2.6 (2.5-2.7)	201/0.2 (0.2-0.3)	935/1.1 (1.0-1.2)	158/3.2 (3.1-3.3)	3084/3.6 (3.5-3.8)
>2	29 579 (2.3)	13/0.6 (0.3-1.1)	37/1.8 (1.3-2.5)	5/0.3 (0.1-0.6)	24/1.2 (0.8-1.8)	2748/2.5 (1.9-3.3)	67/3.3 (2.6-4.2)
Data missing	8826 (0.7)	5/0.9 (0.3-2.2)	16/3.0 (1.7-4.8)	1/0.2 (0.0-1.0)	6/1.1 (0.4-2.4)	16/3.0 (1.7-4.8)	27/4.5 (3.3-7.3)
Apgar score at 5 min							
0-3	2264 (0.2)	1/0.6 (0.0-3.2)	10/5.7 (2.7-10.5)	2/1.1 (0.1-4.1)	4/2.3 (0.6-5.9)	7/4.0 (1.6-8.2)	9/5.1 (2.4-9.7)
4-6	8837 (0.7)	7/1.1 (0.5-2.3)	19/3.1 (1.8-4.8)	1/0.2 (0.0-0.9)	8/1.3 (0.6-2.5)	15/2.4 (1.4-4.0)	29/4.7 (3.1-6.7)
7-10	1 271 464 (97.7)	649/0.7 (0.7-0.8)	2261/2.6 (2.4-2.7)	203/0.2 (0.2-0.3)	966/1.1 (1.0-1.2)	2889/3.3 (3.1-3.4)	3238/3.7 (3.5-3.8)
Data missing	18 957 (1.5)	12/0.7 (0.4-1.3)	43/2.6 (1.9-3.5)	11/0.7 (0.3-1.2)	19/1.2 (0.7-1.8)	62/3.8 (2.9-4.9)	58/3.5 (2.7-4.6)
Sex							
Male	668 592 (51.4)	391/0.8 (0.8-0.9)	725/1.6 (1.4-1.7)	73/0.2 (0.1-0.2)	55/0.1 (0.1-0.2)	1745/3.7 (3.6-3.9)	1975/4.2 (4.0-4.4)
Female	632 930 (48.6)	278/0.6 (0.6-0.7)	1608/3.6 (3.5-3.8)	144/0.3 (0.3-0.4)	942/2.1 (2.0-2.3)	1228/2.8 (2.6-2.9)	1359/3.1 (2.9-3.2)
Parity							
1	93 252 (7.2)	89/1.3 (1.0-1.6)	198/2.8 (2.4-3.2)	15/0.2 (0.2-0.5)	81/1.2 (0.9-1.4)	338/4.8 (4.3-5.4)	317/4.5 (4.0-5.1)
2-3	972 499 (74.7)	430/0.6 (0.6-0.7)	1579/2.3 (2.2-2.4)	87/0.1 (0.2-0.3)	716/1.0 (1.0-1.1)	1906/2.8 (2.7-2.9)	2155/3.1 (3.0-3.3)
≥4	235 771 (18.1)	150/1.0 (0.8-1.1)	556/3.6 (3.3-3.9)	24/0.2 (0.2-0.4)	200/1.3 (1.1-1.5)	729/4.7 (4.4-5.1)	862/5.6 (5.2-6.0)
Maternal age, y							
<17	4240 (0.3)	9/2.4 (1.1-4.5)	24/6.4 (4.1-9.5)	0/0.0 (0.0-0.8)	4/1.1 (0.3-2.7)	37/9.8 (6.9-13.5)	43/11.4 (8.3-15.4)
17-19	62 316 (4.8)	47/0.9 (0.7-1.2)	161/3.2 (2.7-3.7)	11/0.2 (0.1-0.4)	43/0.9 (0.6-1.1)	364/7.2 (6.5-8.0)	350/6.9 (6.2-7.7)
20-24	356 574 (27.4)	187/0.7 (0.6-0.8)	752/2.8 (2.6-3.1)	54/0.2 (0.2-0.3)	244/0.9 (0.8-1.0)	1081/4.1 (3.8-4.3)	1145/4.3 (4.1-4.6)
25-29	486 513 (37.4)	215/0.6 (0.5-0.7)	798/2.3 (2.2-2.5)	76/0.2 (0.2-0.3)	399/1.2 (1.1-1.3)	851/2.5 (2.3-2.6)	1043/3.0 (2.9-3.2)
30-39	376 792 (29.0)	197/0.8 (0.7-1.0)	570/2.4 (2.2-2.6)	74/0.3 (0.2-0.4)	291/1.2 (1.1-1.4)	607/2.6 (2.4-2.8)	721/3.0 (2.8-3.3)
≥40	15 086 (1.2)	14/1.6 (0.9-2.6)	28/3.1 (2.1-4.5)	2/0.2 (0.0-0.8)	16/1.8 (1.0-2.3)	33/3.7 (2.5-5.1)	32/3.6 (2.4-5.0)
Maternal education ^b							
0-2	249 229 (19.2)	168/0.9 (0.8-1.0)	521/2.7 (2.5-3.0)	41/0.2 (0.2-0.3)	183/1.1 (0.8-1.1)	856/4.5 (4.2-4.8)	895/4.7 (4.4-5.0)
3-4	641 018 (49.3)	289/0.7 (0.6-0.7)	1098/2.5 (2.3-2.6)	101/0.2 (0.2-0.3)	448/1.1 (1.0-1.2)	1470/4.3 (3.2-3.5)	1730/3.9 (3.7-4.1)
Higher	400 015 (30.7)	191/0.7 (0.6-0.8)	671/2.5 (2.3-2.7)	68/0.3 (0.2-0.3)	357/1.3 (1.1-1.4)	585/2.2 (2.0-2.4)	647/2.4 (2.2-2.6)
Data missing	11 260 (0.9)	21/2.1 (1.3-3.2)	43/4.3 (3.1-5.8)	7/0.7 (0.3-1.5)	9/0.9 (0.4-1.7)	62/6.3 (4.8-8.0)	62/6.3 (4.8-8.0)
Maternal psychiatric family history							
≥1 diagnosis	7139 (0.6)	9/2.3 (1.1-4.4)	37/9.7 (6.8-13.3)	1/0.3 (0.0-1.5)	9/2.4 (1.1-4.5)	62/16.2 (12.4-20.8)	42/11.0 (7.9-14.8)
No family history	1 294 383 (99.5)	660/0.7 (0.7-0.8)	2296/2.5 (2.4-2.6)	216/0.2 (0.2-0.3)	988/1.1 (1.0-1.2)	2911/3.2 (3.1-3.3)	3292/3.6 (3.5-3.8)

Abbreviations: IR, incidence rate; SDS, standard deviation score.

^aUnadjusted incidence rates per 10 000 person-years.

^bLevel of formal full-time education after compulsory school in the Swedish educational system (0-2: ≥9 years of compulsory education plus up to 2 years of postcompulsory education [upper secondary school]; 3-4: 9 years of compulsory education plus 3-4 years of postcompulsory education; and "higher": 9 years of compulsory education plus >4 years of postcompulsory education).

and Apgar score at 5 minutes, sex, parity, maternal age at delivery, maternal education, and maternal psychiatric family history.

APGAR SCORE

In the crude models, a low Apgar score (0-3) was significantly associated with increased risk of psychiatric hospitalization with depressive disorder and bipolar affective disorder. However, in the adjusted models, this association remained statistically significant only for depressive disorder, where the risk was doubled. Although not statistically significant, the risk of being hospitalized with an eating disorder was tripled in the group with an Apgar score of 0 to 3.

The Wald test was used to assess interactions among the 3 pregnancy outcomes and psychiatric hospitaliza-

tion with all psychiatric diagnostic clusters studied (a collapsed variable). Specifically, the following interactions were investigated: gestational age × Apgar score at 5 minutes, gestational age × small for gestational age, Apgar score at 5 minutes × small for gestational age, and maternal psychiatric history × gestational age. No significant interactions were observed ($P \geq .05$).

COMMENT

This study demonstrates that preterm birth is associated with increased risks of a range of severe mental disorders in adulthood, including nonaffective psychosis, depressive disorder, and bipolar affective disorder, in a monotonic manner. The association between preterm

Table 3. Crude and Adjusted HRs (“Relative Risks”) for Incidence of First Hospitalization With a Selected Psychiatric Diagnosis After an Individual’s 16th Birthday in Relation to Pregnancy Outcomes

Exposure	HR (95% CI)					
	Nonaffective Psychosis		Depressive Disorder		Bipolar Affective Disorder	
	Crude	Fully Adjusted ^a	Crude	Fully Adjusted ^a	Crude	Fully Adjusted ^a
Gestational age, wk						
<32	2.8 (1.2-6.7)	2.5 (1.0-6.0)	3.0 (1.9-4.7)	2.9 (1.8-4.6)	7.2 (2.7-19.6)	7.4 (2.7-20.6)
32-36	1.8 (1.2-2.5)	1.6 (1.1-2.3)	1.4 (1.1-1.7)	1.3 (1.1-1.7)	2.6 (1.6-4.4)	2.7 (1.6-4.5)
37-41	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
≥42	1.0 (0.8-1.2)	1.0 (0.8-1.3)	1.1 (1.0-1.3)	1.1 (1.0-1.2)	1.0 (0.7-1.5)	1.0 (0.7-1.5)
Birth weight for gestational age, SDS						
≤2	1.1 (0.7-1.6)	1.0 (0.7-1.5)	1.1 (0.8-1.3)	1.1 (0.9-1.4)	1.0 (0.5-2.1)	1.0 (0.5-2.0)
-1.99 to 1.99	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
≥2	0.9 (0.5-1.6)	0.9 (0.5-1.5)	0.8 (0.6-1.1)	0.7 (0.5-1.0)	0.9 (0.3-2.4)	0.8 (0.3-2.1)
Apgar score at 5 min						
0-3	0.8 (0.1-5.8)	0.7 (0.1-4.8)	2.4 (1.3-4.4)	2.2 (1.2-4.0)	5.3 (1.3-21.2)	3.8 (0.9-15.5)
4-6	1.6 (0.8-3.4)	1.3 (0.6-2.8)	1.2 (0.8-2.0)	1.1 (0.7-1.7)	0.7 (0.1-5.2)	0.5 (0.1-3.6)
7-10	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]

Exposure	HR (95% CI)					
	Eating Disorders		Drug Dependency		Alcohol Dependency	
	Crude	Fully Adjusted ^a	Crude	Fully Adjusted ^a	Crude	Fully Adjusted ^a
Gestational age, wk						
<32	3.7 (1.4-10.0)	3.5 (1.3-9.6)	1.2 (0.7-2.3)	1.2 (0.6-2.2)	1.5 (0.9-2.3)	1.3 (0.8-2.3)
32-36	1.4 (0.8-2.3)	1.4 (0.9-2.4)	1.3 (1.1-1.6)	1.2 (1.0-1.4)	1.4 (1.2-1.7)	1.3 (1.1-1.5)
37-41	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
≥42	1.2 (0.9-1.5)	1.1 (0.9-1.5)	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.1 (1.0-1.2)	1.1 (1.0-1.2)
Birth weight for gestational age, SDS						
≤2	0.7 (0.4-1.4)	0.7 (0.4-1.3)	1.5 (1.3-1.8)	1.4 (1.2-1.6)	1.3 (1.1-1.5)	1.2 (1.0-1.4)
-1.99 to 1.99	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
≥2	0.7 (0.3-1.6)	0.7 (0.3-1.5)	0.8 (0.6-1.0)	0.8 (0.6-1.1)	0.9 (0.7-1.1)	0.9 (0.7-1.1)
Apgar score at 5 min						
0-3	3.1 (0.8-12.5)	3.0 (0.8-12.3)	1.1 (0.5-2.4)	1.0 (0.4-2.2)	1.5 (0.8-2.9)	1.3 (0.7-2.6)
4-6	1.6 (0.6-4.4)	1.6 (0.6-4.4)	0.8 (0.5-1.3)	0.7 (0.4-1.0)	1.3 (0.9-1.9)	1.1 (0.8-1.6)
7-10	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: HR, hazard ratio; SDS, standard deviation score.

^aThe HRs are adjusted for the other variables in the table and for sex, parity, maternal age at delivery, maternal education, and maternal psychiatric family history.

birth and psychiatric outcomes persisted after adjusting for other pregnancy outcomes previously suggested to be associated with psychiatric disorders (eg, nonoptimal fetal growth and Apgar score),^{24,25} maternal sociodemographic characteristics, and maternal psychiatric history.²⁶ In the adjusted models, being born before week 32 was further associated with a 3-fold increased risk of eating disorders and being born before week 36 with a 30% increased risk of alcohol and 20% increased risk of drug dependency. These results suggest that preterm birth constitutes a single independent risk factor for a range of psychiatric disorders, or at least for the more severe forms of these disorders, as the analysis included data from hospital registers only.

Preterm birth has most frequently been studied in relation to psychiatric disorders with typical onset in childhood and adolescence,^{27,28} and a few studies^{29,30} investigating a range of psychiatric outcomes have reported preterm birth as being a significant risk factor for psy-

chiatric hospitalization. The association between preterm birth and increased risk of adult-onset (defined as ≥16 years of age) schizophrenia is consistent with previous findings,¹¹ but this is the first study to report an association between preterm birth and both depressive disorder and bipolar affective disorder.

The findings regarding bipolar affective disorder are a distinct outlier from the published literature, which reports no significant associations between indicators of fetal growth, including preterm birth, and the risk of bipolar disorder.^{13,31} Several studies (reviewed by Demjaha et al³²) have suggested that impairments in neurodevelopment may distinguish schizophrenia from bipolar disorder. We previously reported that poor school performance, which is a putative marker of neurodevelopment, was associated with preterm birth³³ and also with the risk of any psychosis,³⁴ including bipolar disorder.³⁵ Excellent school performance, on the other hand, was associated with increased risk of bipolar disorder only.³⁵

We speculated that 2 subtypes of bipolar disorder might exist: a neurodevelopmental form associated with cognitive impairment and a nonneurodevelopmental form that may be associated with enhanced cognitive function.³⁵ Individuals with bipolar affective disorder who were born very preterm may represent this neurodevelopmental subtype of bipolar affective disorder.

The lack of specificity in outcome suggests that there may be similar developmental etiologies linking various psychiatric disorders. This evidence for “same risk–different outcome” is in line with results of molecular genetic studies showing common genes for affective and nonaffective psychoses³⁶ and of family studies showing an increased risk of a full spectrum of psychiatric outcomes in offspring with a parental history of psychiatric disorder, including those hitherto not regarded as being clinically related.³⁷ Work on cognitive endophenotypes also suggests an overlap between schizophrenia, bipolar disorder, and other psychiatric disorders.^{34,35,38,39}

Moreover, there is a strong (maternal) genetic component for preterm birth.⁴⁰ However, the present results were essentially unchanged after controlling for maternal psychiatric history, suggesting that preterm birth does not share a genetic etiology with maternal psychiatric disorders.

The theory that preterm birth is associated with impaired neurodevelopment has biological plausibility. The immature nervous system is particularly vulnerable to neonatal brain injury,⁴¹ which may result in alterations of the programmed corticogenesis of the developing brain.⁴² Long-lasting and widespread structural brain alterations have been described after very preterm birth, including in temporal and frontal cortices³ and in specific regions of interest, such as the hippocampus⁴³ and thalamus.⁴⁴ Functional magnetic resonance studies in young adults who were born very preterm have documented neuroanatomical alterations in brain networks that have also been found to be disrupted in psychiatric populations, including frontostriatal,⁴⁵ frontoparietal, occipital,⁴⁶ temporal,⁴⁷ and fronto-parieto-cerebellar.⁴⁸ The increased susceptibility for psychiatric disorders conferred by preterm birth could interact with genetic factors so that specific genetic variants may not be associated with increased vulnerability to psychiatric disorders in the absence of a particular environmental risk.⁴⁹

Alternatively, the association between preterm birth and psychiatric outcomes may be confounded by risk factors,^{50–52} including unmeasured sociodemographic and lifestyle factors (including ethnicity and socioeconomic status^{53,54}), family history of a previous preterm delivery,⁵⁵ smoking,⁵⁵ substance abuse,⁵⁶ bacterial vaginosis, intrauterine bacterial infections,⁵⁷ and viral infections,⁵⁸ which were not controlled for in the present analyses. We previously demonstrated that the offspring of mothers with bipolar disorder are at increased risk for preterm delivery.⁵⁹

The present results show that nonoptimal fetal growth was significantly associated with drug or alcohol dependence. This association may, however, be confounded by maternal characteristics, as smoking and misusing alcohol and drugs are familial and known risk factors for nonoptimal fetal growth, including intrauterine growth restriction.⁶⁰ The present results also show that low Apgar scores at 5 minutes, as well as preterm birth, was significantly

and independently associated with depressive disorder in the adjusted models. Low Apgar scores at 5 minutes were recently found to be associated with a high internalizing score in low-birth-weight adolescents.⁶¹ Although not statistically significant, the risk of being hospitalized with an eating disorder was tripled in the group with low Apgar scores. The failure to obtain statistical significance is probably a consequence of the small number of women with eating disorders and the very low rate of low Apgar scores (0.17%) in the sample.

Strengths of the study include its focus on the association between perinatal complications and a range of adult-onset (defined herein as following an individual's 16th birthday) psychiatric disorders, whereas most previous studies had considered psychiatric disorders with childhood and adolescent onset.^{27,28} Other strengths are the sample size, which is large compared with that of other studies that used similar methods,^{29,30} and the simultaneous inclusion of prenatal and perinatal risk factors, maternal sociodemographic characteristics, and maternal psychiatric family history as potential confounders.

Limitations of this study include the fact that psychiatric diagnoses were studied in relation to hospitalization; hence only the more severe psychiatric cases were included in the analyses. This selection may have affected the reported incidence of disorders, which is relatively lower than the expected rate of incidence of the selected psychiatric disorders in the general population. A further limitation of this study is that controls would have included individuals not hospitalized for the psychiatric disorders we studied and those with psychiatric disorders that often do not require hospitalization, such as anxiety and mood disorders. Another issue concerns the chosen definitions of psychiatric outcomes, such as the inclusion of schizophrenia in the nonaffective psychosis category of the outcomes measures. These issues could potentially limit the generalizability of these results. Another potential limitation of this study is the estimation of gestational age based on the mother's last menstrual period. A more accurate estimation would be provided by the use of ultrasound techniques.⁶² Gestational age derived from last menstrual period typically results in overestimates of gestational age by approximately 2 to 3 days.⁶³ Thus, these results probably underestimate rather than overestimate the association between gestational age and hospitalization with a range of psychiatric diagnoses. Another limitation of this study may be that individuals who were born preterm may be overrepresented in inpatient studies for reasons other than increased psychiatric disorders. Preterm-born individuals may have easier access to hospital care because of increased medical awareness and may be more familiar with the medical setting.⁶⁴ Finally, the cohort was followed up between ages 16 and 29 years only, so the results may apply only to individuals with an age at onset within the narrow time frame we investigated.

The finding of a significant monotonic association between gestational age and later hospital admission with a range of psychiatric diagnoses suggests that future longitudinal research combining gene–environment information, including gestational age, may represent a useful investigative tool with potential for early identification

of individuals who may be particularly vulnerable to develop a variety of psychiatric disorders in late adolescence and young adulthood.

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