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Preterm birth and psychiatric medication prescription in young adulthood: a Swedish national cohort study

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Background Recent studies suggest an increased risk of adverse mental health outcomes among young adults who were born preterm. These studies have been based mainly on hospital data, thus missing large numbers of mental health problems that do not require inpatient treatment. We used national outpatient and inpatient pharmacy data to evaluate whether individuals who were born preterm were more likely to be prescribed psychiatric medications during young adulthood than individuals who were born full term.

Methods A national cohort of all infants born in Sweden from 1973 through 1979 [$N = 635\,933$, including 28 799 who were born preterm (<37 weeks)] was followed to ages 25.5–34.0 years to determine whether psychotropic medications (antidepressants, antipsychotics, anxiolytics, hypnotics/sedatives and/or psychostimulants) were prescribed in 2005–06.

Results A trend of increasing rate of prescriptions for antipsychotics, antidepressants and hypnotics/sedatives in young adulthood was observed by earlier gestational age at birth. Young adults who were extremely preterm at birth (23–27 weeks) were 3.1 times more likely to be prescribed antipsychotics [95% confidence interval (CI) 1.66–5.93], 1.8 times more likely to be prescribed antidepressants (95% CI 1.26–2.64) and 1.8 times more likely to be prescribed hypnotics/sedatives (95% CI 1.15–2.96) than individuals who were full term at birth, after adjusting for potential confounders.

Conclusions This national cohort study, using outpatient and inpatient pharmacy data, suggests that preterm birth has important independent effects on mental health that extend at least into young adulthood.

Keywords Anti-anxiety agents, antidepressive agents, antipsychotic agents, hypnotics and sedatives, premature birth

Introduction

The number of infants born preterm in the USA and other developed countries has increased significantly over the past 10–20 years due in part to improvements in neonatal intensive care and decreases in perinatal morbidity and mortality.[1] The high and increasing rates of premature births constitute a major public health concern as well as a large

cost to society—at least $26 billion a year in the USA according to a 2006 report from the Institute of Medicine of the National Academies.[2] Improvements in neonatal care have been accompanied by increased morbidity in childhood and adolescence.[3] Preterm birth has been associated with complex neurodevelopmental disabilities that become apparent in early childhood,[1,4] and with a wide spectrum of educational and behavioural difficulties that become apparent at school age and may persist into adolescence.[3]

Although much is known about the public health burden of preterm birth in childhood and adolescence, less is known about longer-term mental health outcomes. Previous studies have provided suggestive but inconsistent results on the association between preterm birth or low birth weight and psychiatric disorders.[1,5–17] A recent study reported that preterm birth is associated with increased risk of psychiatric hospitalization in adolescence or early adulthood.[18] That study was based on hospital discharge data, thus missing the greater number of mental illnesses that require medical treatment without hospitalization. The relationship between preterm birth and a wider spectrum of neuropsychiatric outcomes remains poorly elucidated.

The objective of this study was to evaluate whether individuals who were preterm at birth were more likely to be prescribed psychotropic medications in young adulthood than individuals who were full term at birth. In order to evaluate long-term mental health effects in a broad national population, we obtained medication prescription data from nationwide outpatient as well as inpatient pharmacy records in all of Sweden.

Methods

Data sources

This population-based cohort study was based on register data in a national research database, WomMed, financed by the US National Institute of Child Health and Human Development and located at the Centre for Primary Health Care Research, Lund University, Sweden. This database includes annual data from prenatal and birth records, hospital admissions and death records for each mother and child in Sweden. Information on date of delivery, birthweight and length, mode of delivery and maternal and fetal complications is transferred from hospital records, together with prenatal care data, to the Swedish Medical Birth Registry, which is the main register in the WomMed Database.

The WomMed Database also contains individual-level socio-demographic information, including age, marital status, socio-economic status indicators and country of origin, collected annually starting in 1990. For the current study, socio-demographic characteristics were identified using the Swedish Population and Housing Census of 1990, the most recent census when the participants in this study (who were then 11–17 years of age) were still likely to be residing in the same household as their mothers. This census information was used to identify maternal characteristics that would reflect the social conditions of these individuals during their upbringing, and which may be associated with subsequent mental health outcomes. Socio-economic deprivation is a well-established risk factor for premature birth. To the extent that low maternal socio-economic status may have resulted from having given birth to a child prematurely, adjustment for these characteristics would be expected to bias the results conservatively, towards the null hypothesis.

Information on psychotropic medication prescriptions was obtained using a national pharmacy register maintained by the National Board of Health and Welfare. These data were linked to the national Medical Birth Register using an anonymous, serial number version of each individual's unique personal identification number. The national pharmacy register includes a record of each medication that is prescribed by a health-care provider and dispensed directly to a patient by any outpatient or inpatient pharmacy in Sweden. For inpatients, the register includes all medications prescribed and dispensed to a patient upon discharge from the hospital, but not medications directly administered to a patient during the hospital course prior to discharge. The unavailability of data for medications administered during a hospital course is non-differential with respect to preterm birth status and would also be expected to bias the results towards the null hypothesis.

All pharmacy data are categorized according to the Anatomical Therapeutic Chemical (ATC) Classification System developed by the WHO Collaborating Centre for Drug Statistics Methodology. We obtained information on medication prescriptions for conditions of the nervous system (code N), which were further subclassified as antipsychotics (N05A), anxiolytics (N05B), hypnotics/sedatives (N05C), antidepressants (N06A) and psychostimulants (N06B).

Study population

A total of 699 650 women and men, born 1973 through 1979, were identified in the Swedish Medical Birth Registry. For each individual, we identified the gestational age at birth based on maternal report of last menstrual period. An anonymous, serial-number version of the personal identification number of the mother (similar to the US social security number) was used to link mothers to offspring and to determine maternal age at the time of each individual's birth. A total of 11 695 (1.7%) individuals died prior to 2005 (when the national pharmacy register was started) and were excluded from the current analysis. Approximately half of these deaths occurred within the first year of life. Of the remaining

individuals, we excluded 39 106 (5.6%) who had moved away from Sweden prior to 2005, 573 (0.1%) who had missing information on gestational age at birth and 7995 (1.2%) who had significant congenital anomalies (i.e. other than undescended testicle, preauricular appendage, congenital nevus or hip dislocation). In order to remove possible coding errors, 4342 (0.6%) individuals were excluded who had a birthweight >3 standard deviation (SD) above the mean or <6 SD below the mean for gestational age and sex, and 6 (<0.01%) were excluded who had a reported gestational age <23 weeks. A total of 635 933 individuals (90.9% of the original cohort) remained for inclusion in the analysis.

Study period

All study participants, born 1973 through 1979, were followed up for prescription of psychotropic medications from 1 July 2005 through 31 December 2006, the first 1.5 years that the national pharmacy register was kept. These individuals were between 25.5 and 34.0 years of age during the period of follow-up.

Independent variables

Infant's gestational age at birth. This variable was categorized as 23–27, 28–32, 33–34, 35–36, 37–42 (full term) and ⩾43 weeks. Near-term births were stratified into finer categories (33–34 and 35–36 weeks) in order to provide more detail for this range in which there may be discretion by the physician on the timing of delivery.

Infant's date of birth. Infant's date of birth was modelled as a continuous variable. We adjusted for this to control for differences by age and for changes in prenatal or neonatal care that may have occurred during the study period.

Infant's gender. *Maternal age at birth of child*. Modelled as a continuous variable.

Maternal immigration status. 'Born in Sweden', 'immigrated from Finland' or 'immigrated from another country'.

Maternal marital status in 1990. 'Married/cohabiting', 'never married', 'divorced' or 'widowed'.

Maternal occupation in 1990. 'Unskilled worker', 'skilled worker', 'professional', 'white collar', 'other occupations' or 'unknown'.

Maternal income in 1990. Calculated as the mother's annual family income divided by the number of people in the family, or family income per capita, using a weighted system whereby small children are given lower weights than adolescents and adults. The final variable was categorized in quartiles.

Maternal education in 1990. 'Compulsory high school or less (⩽9 years)', 'practical high school or some theoretical high school (10–11 years)' or 'theoretical high school and/or college (⩾12 years)'.

Paternal education in 1990. 'Compulsory high school or less (⩽9 years)', 'practical high school or some theoretical high school (10–11 years)' or 'theoretical high school and/or college (⩾12 years)'.

Maternal region of residence in 1990. 'Large city', 'medium city' or 'small city or rural area'. We adjusted for this variable because it may be associated with access to prenatal care, and to psychiatric care in young adulthood.

Maternal time lived at current residence as of 1990. Dichotomized to <5 years or ⩾5 years.

Maternal prescription of psychotropic medications. We adjusted for whether the mothers of the study participants were prescribed psychotropic medications (antipsychotics, antidepressants, anxiolytics, hypnotics/sedatives and/or psychostimulants) during the follow-up period (1 July 2005 through 31 December 2006). Each of these medication groups was entered into the model separately and dichotomized to 'no prescriptions' or 'one or more prescriptions'.

Maternal hospitalization for mental disorders. We adjusted for whether the mothers of the study participants were ever hospitalized for a mental disorder (ICD-9 codes 290–319, ICD-10 codes F00–F99 or the equivalent coding in earlier ICD versions) from 1 January 1964 through 31 December 2006, dichotomized to 'never' or 'ever' hospitalized for a mental disorder.

Outcome variables

The outcome of interest was one or more prescriptions of a psychotropic medication dispensed at any outpatient or inpatient pharmacy in Sweden during the follow-up period (1 July 2005 through 31 December 2006). This outcome was evaluated separately for each of the following medication groups: antipsychotics, antidepressants, anxiolytics, hypnotics/sedatives and psychostimulants. In addition, we evaluated the outcome of one or more prescriptions in 'any of the above' medication groups.

We also evaluated oral contraceptive prescription as a 'control medication'. Oral contraceptive use in young adulthood would not a priori be expected to be associated with preterm birth status. If an association were found between preterm birth and psychotropic medications in young adulthood, and not between preterm birth and oral contraceptive use in young adulthood, the association with psychotropic medications would be less likely to be due to an artifact in the data or diagnostic bias among individuals who were born preterm. Oral contraceptive prescription was dichotomized as 'never' or 'ever' during the same follow-up period as above.

Statistical analysis

Multivariate logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between gestational age at birth (categorized as 23–27, 28–32, 33–34, 35–36, 37–42, ⩾43 weeks) and prescription of psychotropic medication (one or more vs none) in young adulthood (ages

25.5–34.0 years), using full-term birth (37–42 weeks) as the reference category. Analyses were conducted unadjusted, and then were adjusted for infant and maternal characteristics that are potential confounders (infant date of birth, infant gender, maternal age at the birth of the child, maternal immigration status, maternal marital status, maternal occupation, maternal income, maternal education, paternal education, maternal region of residence, maternal time lived at current residence, maternal prescription of psychotropic medications during the follow-up period, and maternal hospitalization for a mental disorder from 1964 through 2006). We explored for interaction effects between gestational age at birth and each of these infant and maternal characteristics with respect to prescription of psychotropic medication in young adulthood, using a likelihood ratio test to evaluate for statistical significance. All analyses were conducted using Stata statistical software, version 9.1.[20]

Results

Infant and maternal characteristics are presented by gestational age at birth in Table 1. Of the 635 933 individuals who were identified, 28 799 (4.5%) were born prematurely (<37 weeks). Among these, 263 (0.04%) were born at 23–27 weeks; 3367 (0.5%) were born at 28–32 weeks; 5822 (0.9%) were born at 33–34 weeks; and 19 345 (3.0%) were born at 35–36 weeks. Compared with individuals who were born full or post-term, those who were born prematurely were more likely to be male, and their mothers were more likely to have immigrated to Sweden, be unmarried, be less educated, have lower income, be prescribed psychotropic medications and/or be hospitalized for a mental disorder.

Table 2 presents, by gestational age at birth, the percentage of young adults (ages 25.5–34.0 years) who were prescribed and dispensed one or more psychotropic medications during the follow-up period. For each of the psychotropic medication groups, individuals who were born full term had the lowest prevalence of medication prescription in young adulthood. A trend of increasing prevalence of prescription was observed for antipsychotics, hypnotics/sedatives and possibly anxiolytics, by earlier gestational age at birth across all gestational ages <37 weeks, and for antidepressants at gestational ages <33 weeks. For oral contraceptives (analysed as a control medication), the highest prevalence of prescription in young adulthood was observed for women who were born at gestational ages 23–27 weeks, but unlike the relationship for psychotropic medications, no trend was observed across gestational age groups.

Table 3 presents ORs and 95% CIs for the association between gestational age at birth and prescription of psychotropic medications in young adulthood. Individuals who were born prematurely were more likely to be prescribed antipsychotics, antidepressants, hypnotics/sedatives or anxiolytics in young adulthood compared with individuals who were born full term. After adjusting for potential confounders (see Table 3 footnote), individuals who were born at a gestational age of 23–27 weeks were 3.1 times (95% CI 1.66–5.93) more likely to be prescribed antipsychotics, 1.8 times (95% CI 1.26–2.64) more likely to be prescribed antidepressants and 1.8 times (95% CI 1.15–2.96) more likely to be prescribed hypnotics/sedatives than individuals who were full term at birth. A trend of increasing risk by earlier gestational ages was observed across all gestational age groups <37 weeks for antipsychotics and hypnotics/sedatives and at gestational ages <33 weeks for antidepressants.

For oral contraceptives (analysed as a control medication), the largest OR among all gestational age groups was observed for individuals born at 23–27 weeks (adjusted OR 1.24; 95% CI 0.87–1.76). This risk estimate, however, was smaller than the corresponding ORs in this gestational age group for any of the psychotropic medications studied. Furthermore, unlike the relationships found for psychotropic medications, no trend was observed across a broader range of gestational ages.

Among the adjustment variables, the most important confounding factors were maternal marital status, maternal occupation and maternal income. In general, individuals whose mothers were unmarried, skilled or unskilled workers and/or had low income were more likely to be born prematurely and to be prescribed psychotropic medications in young adulthood than other individuals. Adding any combination of other variables included in Table 1 had little effect on the OR estimates.

Exploratory analyses for interactions between infant or maternal characteristics and gestational age with respect to psychotropic medication prescription revealed only one interaction with a P-value <0.01. This interaction indicated that the risk of antidepressant prescription in individuals born at a gestational age of 23–27 weeks compared with those born at full term was greater among individuals whose mothers had immigrated from Finland (OR 2.47; 95% CI 0.71–8.62) or from another country (OR 2.95; 95% CI 0.99–8.79) than among those with Swedish-born mothers (OR 1.59; 95% CI 1.08–2.34).

Discussion

This national cohort study used outpatient and inpatient pharmacy data to evaluate whether individuals who were born preterm are more likely to be prescribed psychotropic medications during young adulthood than individuals who were born full term. We found that earlier gestational age at birth was associated with increased risk of prescription of antipsychotics, antidepressants, hypnotics/sedatives and

Table 1 Infant and maternal characteristics by gestational age at birth (1973–79)

	Gestational age in weeks, %					
	23–27 ($N=263$)	28–32 ($N=3367$)	33–34 ($N=5822$)	35–36 ($N=19\,347$)	37–42 ($N=588\,410$)	⩾43 ($N=18\,724$)
Infant's gender						
Male	51.7	56.2	55.7	55.2	51.2	50.1
Female	48.3	43.8	44.3	44.8	48.8	49.9
Maternal age at birth of child (years)						
<18	2.3	3.3	2.9	2.3	1.4	1.9
18–24	38.0	36.8	35.8	35.3	34.9	41.4
25–34	50.6	51.5	52.9	54.3	57.7	53.2
⩾35	9.1	8.4	8.4	8.1	6.0	3.6
Maternal immigration status						
Born in Sweden	85.6	87.9	88.4	89.3	91.1	92.0
Immigrated from Finland	6.5	5.3	4.8	4.7	4.2	4.0
Immigrated from another country	8.0	6.8	6.8	5.9	4.7	4.1
Maternal marital status in 1990						
Married/cohabiting	68.2	69.7	70.3	72.0	76.4	72.9
Never married	15.9	13.6	12.8	11.7	9.5	11.5
Divorced	15.1	15.7	15.7	14.8	13.0	14.6
Widowed	0.8	1.0	1.2	1.5	1.2	1.0
Maternal occupation in 1990						
Unskilled worker	16.4	20.9	21.0	22.5	25.9	23.5
Skilled worker	17.1	16.2	15.9	16.7	18.2	17.4
Professional	7.6	9.3	8.9	9.3	9.4	9.6
White collar	27.4	29.3	30.1	29.1	27.4	28.8
Other occupations	11.8	9.4	9.2	9.0	8.5	9.1
Unknown	19.8	14.9	14.9	13.4	10.5	11.7
Maternal income in 1990						
Lowest quartile	36.5	28.7	27.7	26.1	23.0	24.2
Second quartile	20.5	25.3	24.8	25.8	25.7	25.3
Third quartile	24.7	24.6	24.7	25.0	25.7	25.8
Highest quartile	18.3	21.5	22.7	23.1	25.6	24.8
Maternal education in 1990 (years)						
Compulsory high school or less (⩽9)	36.1	31.4	32.1	30.9	26.9	29.5
Practical high school or some theoretical high school (10–11)	44.2	46.8	47.2	46.4	47.2	47.4
Theoretical high school and/or college (⩾12)	19.8	21.8	20.7	22.7	25.9	23.1
Paternal education in 1990 (years)						
Compulsory high school or less (⩽9)	33.7	34.2	36.0	35.0	32.5	34.3
Practical high school or some theoretical high school (10–11)	45.8	44.3	43.6	43.5	43.5	44.5
Theoretical high school and/or college (⩾12)	20.5	21.5	20.4	21.5	24.1	21.2

(continued)

Table 1 Continued

	Gestational age in weeks, %					
	23–27 ($N=263$)	28–32 ($N=3367$)	33–34 ($N=5822$)	35–36 ($N=19\,347$)	37–42 ($N=588\,410$)	⩾43 ($N=18\,724$)
Maternal region of residence in 1990						
Large city	32.3	30.5	29.4	29.7	29.1	29.9
Medium city	34.6	35.1	38.2	37.3	36.9	37.3
Small city or rural area	33.1	34.3	32.4	33.0	34.0	32.8
Maternal time lived at current residence as of 1990 (years)						
<5	25.2	24.3	24.9	23.5	21.2	23.7
⩾5	74.8	75.7	75.1	76.5	78.8	76.3
Maternal prescription of psychotropic medications from 1 July 2005 through 31 December 2006						
Antidepressants	12.9	13.2	11.9	13.3	12.4	12.9
Antipsychotics	2.3	2.5	2.0	2.3	1.7	1.6
Anxiolytics	9.5	7.7	7.6	8.1	6.8	7.0
Hypnotics/sedatives	14.1	14.3	12.5	13.1	12.1	12.6
Psychostimulants	0.0	0.1	0.1	0.1	0.1	0.1
Any of the above	24.3	24.4	22.5	24.4	22.4	23.0
Maternal hospitalization for a mental disorder from 1 January 1964 through 31 December 2006	11.0	11.6	10.3	9.6	7.1	8.4

Table 2 Prescription of psychotropic medications in young adulthood (ages 25.5–34.0 years) by gestational age at birth (1973–79)

	Gestational age in weeks, %					
	23–27 ($N=263$)	28–32 ($N=3367$)	33–34 ($N=5822$)	35–36 ($N=19\,347$)	37–42 ($N=588\,410$)	⩾43 ($n=18\,724$)
Medication group						
Antipsychotics	3.8	2.1	1.5	1.4	1.0	1.1
Antidepressants	12.6	8.8	7.0	7.2	6.8	7.3
Hypnotics/sedatives	7.2	4.9	4.5	4.2	3.6	3.7
Anxiolytics	4.9	4.9	4.1	3.7	3.2	3.4
Psychostimulants	0.4	0.3	0.2	0.2	0.2	0.2
Any of the above	18.3	14.3	12.3	11.8	10.7	11.5
Oral contraceptives (control medication)	22.8	18.1	19.2	19.2	21.2	20.7

possibly anxiolytics at ages 25.5–34.0 years. These associations remained after adjusting for potential confounders, suggesting that preterm birth is an independent risk factor for mental disorders at least into young adulthood.

These findings are consistent with those of a recent study that reported an association between preterm birth and psychiatric hospitalization. Lindstrom *et al*. reported a stepwise increase in risk of psychiatric hospitalization at ages 8–29 years by earlier gestational age at birth.[18]

Preterm birth has multiple causes, which have been described previously.[21–24] Determinants may include chronic stress via activation of the maternal and fetal hypothalamic–pituitary–adrenal (HPA) axis,[25] decidual chorioamniotic inflammation caused by bacterial vaginoses,[26,27] decidual vasculopathy caused by maternal hypertension, preeclampsia and vascular lesions[28,29] and other risk factors such as smoking, undernutrition and diabetes.[28–30] Several studies have reported structural brain sequelae of preterm birth, including reduced cerebral volume in childhood or adolescence,[31–33] and have shown that the degree of preterm birth was a major predictor of altered cerebral volume.[34]

Proposed mechanisms for the effect of preterm birth on neuropsychiatric disorders include a disturbance of the programmed corticogenesis of the developing

Table 3 ORs for association between gestational age at birth (1973–79) and prescription of psychotropic medications in young adulthood (ages 25.5–34.0 years)

Medication group (outcome variable)	Gestational age in weeks (predictor variable)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Antipsychotics	23–27	3.77 (2.00–7.09)	3.14 (1.66–5.93)
	28–32	2.02 (1.60–2.57)	1.77 (1.39–2.25)
	33–34	1.41 (1.14–1.75)	1.28 (1.03–1.58)
	35–36	1.36 (1.20–1.54)	1.25 (1.11–1.41)
	37–42	1.00	1.00
	⩾43	1.05 (0.91–1.21)	1.01 (0.87–1.16)
Antidepressants	23–27	1.98 (1.38–2.86)	1.82 (1.26–2.64)
	28–32	1.33 (1.18–1.50)	1.28 (1.14–1.45)
	33–34	1.05 (0.95–1.16)	1.03 (0.93–1.14)
	35–36	1.08 (1.02–1.14)	1.05 (1.00–1.11)
	37–42	1.00	1.00
	⩾43	1.09 (1.03–1.15)	1.05 (0.99–1.11)
Hypnotics/sedatives	23–27	2.12 (1.33–3.38)	1.84 (1.15–2.96)
	28–32	1.40 (1.20–1.64)	1.29 (1.10–1.52)
	33–34	1.29 (1.14–1.46)	1.22 (1.08–1.39)
	35–36	1.20 (1.12–1.29)	1.15 (1.07–1.23)
	37–42	1.00	1.00
	⩾43	1.06 (0.98–1.14)	1.00 (0.92–1.08)
Anxiolytics	23–27	1.55 (0.89–2.71)	1.36 (0.77–2.38)
	28–32	1.54 (1.31–1.80)	1.43 (1.22–1.68)
	33–34	1.29 (1.13–1.47)	1.22 (1.07–1.40)
	35–36	1.13 (1.05–1.22)	1.08 (1.00–1.17)
	37–42	1.00	1.00
	⩾43	1.05 (0.97–1.13)	1.00 (0.92–1.08)
Psychostimulants	23–27	2.27 (0.32–16.17)	2.05 (0.29–14.68)
	28–32	1.95 (1.07–3.53)	1.76 (0.97–3.20)
	33–34	1.43 (0.84–2.43)	1.35 (0.80–2.29)
	35–36	1.11 (0.79–1.54)	1.03 (0.74–1.44)
	37–42	1.00	1.00
	⩾43	1.05 (0.74–1.48)	1.01 (0.71–1.43)
Any of the above	23–27	1.87 (1.36–2.55)	1.70 (1.24–2.34)
	28–32	1.39 (1.26–1.53)	1.33 (1.21–1.47)
	33–34	1.17 (1.09–1.27)	1.14 (1.05–1.24)
	35–36	1.12 (1.07–1.17)	1.09 (1.04–1.14)
	37–42	1.00	1.00
	⩾43	1.08 (1.03–1.13)	1.04 (0.99–1.09)
Oral contraceptives (control medication)	23–27	1.10 (0.82–1.47)	1.24 (0.87–1.76)
	28–32	0.82 (0.75–0.90)	0.93 (0.84–1.03)
	33–34	0.88 (0.83–0.94)	1.01 (0.93–1.09)
	35–36	0.88 (0.85–0.92)	0.98 (0.94–1.03)
	37–42	1.00	1.00
	⩾43	0.97 (0.94–1.01)	0.97 (0.93–1.02)

[a]Adjusted for infant's date of birth, infant's gender, maternal age at birth of child, maternal immigration status, maternal marital status, maternal occupation, maternal income, maternal education, paternal education, maternal region of residence, maternal time lived at current residence, maternal prescription of psychotropic medications (antipsychotics, antidepressants, anxiolytics, hypnotics/sedatives and/or psychostimulants) during the follow-up period and maternal hospitalization for a mental disorder from 1964 through 2006.

brain. The HPA axis may be involved in the timing of parturition,[35] and altered HPA hormonal activity has been reported in psychiatric disorders such as depression.[36] Genetic mechanisms may also be involved: mothers with psychiatric conditions may have an increased risk of preterm delivery due to HPA hormonal alterations, and their children may be more likely to develop psychiatric conditions due to the hereditary component of these disorders.[37]

The current study has several limitations as well as important strengths. Limitations include, first, the inability to exclude diagnostic bias. It is possible that individuals who were born preterm were more likely to be prescribed psychotropic medications

because of greater contact with the health-care system for other medical conditions. We explored this possibility by analysing oral contraceptive prescription in young adulthood as a 'control medication'. Compared with the associations observed between preterm birth and psychotropic medications in young adulthood, a much weaker relationship and no trend across gestational age groups was observed for oral contraceptives. These findings make it less likely that the observed associations between preterm birth and psychotropic medications are attributable to an artifact in the data or diagnostic bias among individuals who were born preterm. Secondly, the pharmacy data used in this study were available for only 1.5 years of follow-up. Thirdly, estimation of gestational age was based on maternal report of last menstrual period rather than by ultrasound, which was not yet widely used at the time these study participants were born (1973–79).

This study also has several important strengths. The availability of national outpatient as well as inpatient pharmacy data allowed us to incorporate a broad spectrum of mental illness including the large majority of cases that do not require hospitalization. This enabled a more comprehensive assessment of preterm birth and psychiatric outcomes, which is closer to the biologic relationships of interest. Linkage of these pharmacy data to national birth, hospital and census records enabled us to include a broad set of infant and maternal characteristics, including maternal psychiatric medications and psychiatric hospitalizations, in order to adjust for potential confounders. We also evaluated several different classes of psychotropic medications, among which antipsychotic medications had the strongest association with preterm birth status. The differential risks we observed among these medication groups need further replication in future studies.

In summary, these findings from a large national cohort suggest that preterm birth has important independent effects on mental health that extend at least into young adulthood. Further research is needed to clarify the biologic mechanisms by which preterm birth may affect longer-term mental health, including the differential risks for different psychiatric disorders.

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KEY MESSAGES

- This national cohort study used outpatient and inpatient pharmacy data to evaluate whether individuals who were born preterm were more likely to be prescribed psychotropic medications during young adulthood than individuals who were born full term.
- A trend of increasing rate of prescriptions of antipsychotics, antidepressants and hypnotics/sedatives in young adulthood was observed by earlier gestational age at birth, after adjusting for potential confounders.
- These findings suggest that preterm birth has important independent effects on mental health that extend at least into young adulthood.

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