Original Investigation

Gestational Influenza and Bipolar Disorder in Adult Offspring

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IMPORTANCE Gestational influenza has been associated previously with schizophrenia in offspring, but the relationship between this exposure and bipolar disorder (BD) is unclear. The identification of gestational influenza as a risk factor for BD may have potential for preventive approaches.

OBJECTIVE To test the hypothesis that maternal influenza during pregnancy is related to BD among offspring.

DESIGN Nested case-control study of a population-based birth cohort from the Child Health and Development Study (CHDS). From January 1, 1959, through December 31, 1966, the CHDS recruited nearly all pregnant women receiving obstetric care from the Kaiser Permanente Medical Care Plan, Northern California Region (KPNC). Data on treated maternal influenza from the CHDS were used. Potential cases with BD from the cohort were identified by database linkages of identifiers among the CHDS, Kaiser Permanente database, and a large county health care database; by a mailed questionnaire to the CHDS cohort with subsequent interviews; and from an earlier psychiatric follow-up study on this birth cohort.

SETTING The CHDS, Kaiser Permanente, and county health care databases.

PARTICIPANTS Cases of BD (n = 92) confirmed by structured research interviews and consensus diagnosis among the 214 subjects (48% of those ascertained) who participated and control subjects (n = 722) matched on date of birth, sex, and membership in KPNC or residence in Alameda County.

EXPOSURES Influenza.

MAIN OUTCOME AND MEASURES Bipolar I or II disorder, BD not otherwise specified, or BD with psychotic features.

RESULTS We found a significant, nearly 4-fold increase in the risk of BD (odds ratio, 3.82 [95% CI, 1.58-9.24; *P* = .003]) after exposure to maternal influenza at any time during pregnancy. The findings were not confounded by maternal age, race, educational level, gestational age at birth, and maternal psychiatric disorders.

CONCLUSIONS AND RELEVANCE Maternal influenza may be a risk factor for BD. Although replication is required, the findings suggest that prevention of maternal influenza during pregnancy may reduce the risk of BD.

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Maternal influenza has been associated previously with schizophrenia in offspring in a number of studies.[1,2] In the present investigation, we examined the relationship between this infection during pregnancy and the occurrence of bipolar disorder (BD). This hypothesis was based on several observations in the literature. First, some evidence suggests that patients with BD are more likely to be born during the winter and early spring.[3] Second, in the British Perinatal Mortality Survey,[4] influenza and pyrexia were reported more frequently during pregnancy by mothers of patients with affective psychosis compared with control subjects, although limitations of that study included diagnoses based on case notes, no differentiation of the manic depressive phenotype from depressive psychosis, and a small sample size. Third, subjects who were in utero during the second trimester at the time of the 1957 A2/Singapore influenza pandemic manifested a significant increase in the prevalence of major affective disorder, with a similar although nonsignificant ($P > .05$ as reported by the authors) elevation in BD prevalence.[5] That study was limited, however, by exposure misclassification, given that the exposure was defined by ecologic data rather than by infection in individual pregnancies. Another study, which used maternal recall of gestational influenza after diagnosis of BD in offspring, reported a numerical although nonsignificant increase in the risk of BD ($P = .09$).[6]

Moreover, an additional epidemiological study[7] failed to support the hypothesized association. In that study of expectant mothers who attended antenatal clinics in Dublin, Ireland, during the 1957 influenza pandemic, adult offspring whose mothers reported influenza were no more likely to develop BD 34 years later compared with those whose mothers reported no influenza during pregnancy. As noted by the authors,[7] that study was limited by exposure misclassification due to inaccurate diagnosis of influenza and poor recall and by the small number of identified cases.

Consequently, we sought to examine whether maternal influenza increased the risk of BD by capitalizing on a nested case-control study in a well-defined, population-based birth cohort followed up throughout the risk period for development of BD. To address the potential for retrospective bias, maternal influenza during pregnancy was documented as part of the Child Health and Development Study (CHDS) through abstraction of medical records for diagnoses made by physicians; medical records were available for virtually all cohort members. Bipolar disorder was determined by direct, structured research-based interviews of all subjects with consensus diagnosis.

Methods

Description of the Cohort

Cases and controls were drawn from the CHDS birth cohort.[8] From January 1, 1959, through December 31, 1966, the CHDS recruited nearly all pregnant women receiving obstetric care from the Kaiser Permanente Medical Care Plan, Northern California Region (KPNC) in Alameda County. Their live-born offspring (n = 19 044) were automatically enrolled in the KPNC. Comprehensive data were collected prospectively from maternal medical records, maternal interviews, and other sources. Approximately 30% of the population of the county was enrolled in the KPNC. The KPNC membership was largely representative of the population of the Bay Area of California at the time, although extreme incomes were underrepresented. This birth cohort has been studied extensively for prenatal and other early developmental risk factors for schizophrenia.[9] Maternal influenza vaccination was administered to only a small proportion of the sample (6.1%).

Definition of Exposure

The primary exposure investigated in this study was influenza. Diagnoses of influenza during pregnancy in the CHDS data set, which were systematically entered, were extracted from maternal medical records using codes from the *International Classification of Diseases, Ninth Revision* (*ICD-9*). Codes included physician-diagnosed infections, based on results of a physical examination and symptoms of influenza, from 6 months before each gravida's last menstrual period (LMP) to the time of delivery.

In a secondary analysis, we examined the relationship between other maternal infections of the upper or lower respiratory tract, obtained by the same method as for influenza, and BD. Given the small number of individual infections, these were defined as a group. This group of infections consisted of tuberculosis, diphtheria, pertussis, cold, sinusitis, tonsillitis, bronchopneumonia, pneumonia, bronchitis, quinsy, rhinitis, pharyngitis, tracheitis, laryngitis, or empyema.

The exposure periods were (1) periconceptional (30 days before to 30 days after the LMP); (2) first trimester (31-97 days after the LMP); (3) second trimester (98-187 days after the LMP); and (4) third trimester (≥188 days after the LMP until delivery).

Case Ascertainment and Diagnosis

Cases with potential *DSM-IV-TR* BD (bipolar I disorder [BD I], bipolar II disorder [BD II], BD not otherwise specified, and BD with psychotic features) were ascertained by screening procedures from the following 3 sources: the KPNC electronic medical records database, the Alameda County Behavioral Health Care Services (ABHCS) database, and a mailing to the entire living CHDS birth cohort (mothers and children). These 3 methods were used to maximize ascertainment of individuals with BD. Members of the CHDS cohort who belonged to KPNC at the first date of treatment would have been ascertained from the KPNC database. Subjects who left the KPNC before the first treatment of BD and who did not have other health insurance but still lived in Alameda County likely would have been treated by ABHCS if they sought treatment. Subjects who were not ascertained by these 2 approaches were ascertained by a mailed survey. These methods of ascertainment are described in full below.

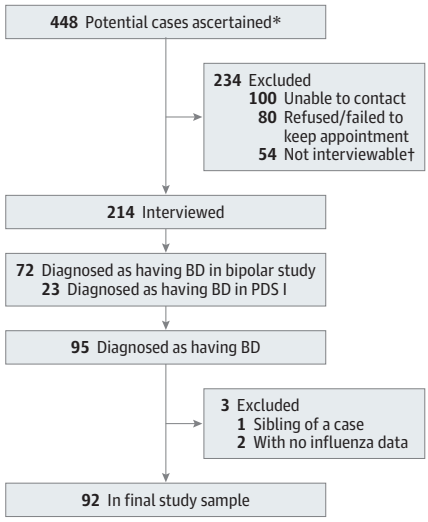
Ascertainment by KPNC

Subjects with potential BD (and other psychotic disorders) were identified by screening the inpatient and outpatient databases of KPNC. Computerized record linkages between CHDS

and KPNC identifiers were conducted on these databases. The inpatient database included all psychiatric hospitalizations of KPNC members, whether in the KPNC or as referrals to non-KPNC hospitals, and covered the period from January 1, 1981, through December 31, 2010 (maximum duration of follow-up was 29 years). Subjects from the KPNC inpatient database have positive findings for potential BD based on discharge diagnoses of *ICD-9* codes 295 through 298. A database of outpatient treatment was introduced in 1981 but did not contain searchable codes for diagnoses until 1995. Potential BD cases from the outpatient database were considered to have positive findings if they received diagnoses identified by *ICD-9* codes 295 through 298, excluding unipolar major depressive disorder. Case ascertainment was complemented by the KPNC outpatient pharmacy database, which commenced in 1992. Screen-positive cases ascertained from this source were based on prescriptions for mood-stabilizing medications used in the treatment of BD (ie, lithium carbonate, carbamazepine, and valproic acid). Before contacting subjects who were currently enrolled in KPNC, the subject's treating psychiatrist was reached, informed about the study, and asked to approve contact with the subject to seek his or her consent to participate.

Subjects identified by any of these methods were invited to participate in the study by letters to the most recent address, and those who did not refuse contact by returning a postcard were contacted to arrange an appointment for a diagnostic interview. Several repeated appointments were scheduled for subjects who failed to attend the interview. Extensive efforts were made to locate individuals who were no longer living at the most recent listed address, including use of Department of Motor Vehicles records, telephone directories, and the subjects' parents or siblings from CHDS or KPNC files. Mortality records, reverse directories, jail searches, and visits to previous addresses were also used as necessary.

Figure. Ascertainment of the Study Sample With Bipolar Disorder (BD)



*We used database linkages with the Kaiser Permanente Medical Care Plan, Northern California Region (KPNC), the Alameda County Behavioral Health Care Services (ABHCS) (described in the Methods section), and subjects from the Child Health and Development Study (CHDS) cohort with screen-positive findings after a mailed questionnaire on mental health to mothers and offspring. We found overlap among the KPNC, ABHCS, and CHDS mailing sources and the Prenatal Determinants of Schizophrenia Study (PDS I). For each source, the numbers of cases found in at least 1 other source among the total number of cases were as follows: 22 of 50 in the KPNC, 14 of 24 in the ABHCS, 11 of 30 in the CHDS mailing, and 18 of 26 in the PDS I. For subjects ascertained on the basis of mailing to mothers and offspring in the CHDS cohort, surveys indicating mental health problems were returned by 535 subjects. Among these, the Family Interview for Genetic Studies was completed on 376 subjects, and of these, 80 subjects had positive findings for bipolar disorder or psychosis. All 80 were sought for interview.

†Reasons include being deceased, incarcerated, or too ill (psychosis, severe mental disability) and not having permission from the physician.

Ascertainment by ABHCS Database

Subjects with potential BD treated as outpatients were also ascertained by electronic record linkage between the CHDS and ABHCS identifiers; the ABHCS database included treatment from January 1, 1993, through December 31, 2009, and thus the maximum duration of follow-up from this source was 16 years. Screen-positive findings in these subjects were based on outpatient diagnoses consisting of *ICD-9* codes 295 through 298, excluding unipolar major depressive disorder. Procedures for recruitment and location of subjects were similar to those described for ascertainment by the KPNC database.

Ascertainment of CHDS Birth Cohort by Mailed Questionnaire and Follow-up

The third method of ascertainment was initiated by letters mailed to all living mothers (n = 6971) and cohort members (n = 13 009) with known addresses in the entire CHDS cohort (excluding families in which potential cases had already been identified in the KPNC and/or the ABHCS database) along with a questionnaire on mental and physical health. This protocol was conducted from 2009 through 2011. Questionnaire respondents who reported "mental health problems" in an eligible cohort member (including the respondent) were contacted by a trained KPNC study interviewer (described in the Diagnostic Protocol subsection), who administered the Family Interview for Genetic Studies to screen for possible BD or psychotic illness in the cohort member. If the interview indicated the presence of at least 1 bipolar and/or psychotic symptom (eg, delusions or hallucinations), the cohort member was considered to have a screen-positive finding and was invited to participate in the diagnostic interview. If the respondent (mother or sibling) described symptoms in a birth cohort member, the respondent was asked whether he or she would be willing to have the study contact the affected family member about participation in the study. If the respondent agreed, the affected cohort member was contacted by letter and invited to participate. We ascertained a total of 448 potential cases of BD and psychotic disorder from these 3 sources (KPNC, ABHCS, and CHDS cohort mailing) (**Figure**).

Diagnostic Protocol

We sought all potential cases from the ascertainment procedures to schedule a diagnostic interview using the Structured Clinical Interview for *DSM-IV-TR* (SCID-I/P).[10] A total of 214 subjects (47.8% of those ascertained) were interviewed. The reasons that interviews were not conducted are delineated in the

Figure. Study interviewers (A.S.B.) were required to have a minimum of a master's degree in a mental health field and were trained to reliability on this instrument. The *DSM-IV-TR* diagnoses including diagnostic qualifiers representing subtypes of BD were systematically assigned by consensus of 3 experienced clinicians (psychiatrists [A.S.B.] or a doctorate-level psychologist) based on review of the SCID-I/P and medical records. This protocol yielded 72 total BD cases. Among those patients interviewed, consensus diagnoses of non-BD disorders were also assigned, including schizophrenia and other schizophrenia spectrum disorders (n = 61), major depressive disorders (n = 62), and other diagnoses (n = 19). These non-BD categories were not included in the present study. Although unipolar major depressive disorder was not included in the screening procedure, the diagnostic protocol enabled us to exclude subjects with database diagnoses of BD and/or psychotic disorders who were found instead to have unipolar depressive disorder in accord with structured research criteria.

Ascertainment From a Previous Study

Additional cases of BD ascertained through KPNC records by an earlier study (Prenatal Determinants of Schizophrenia Study [PDS I])[9] were included in the present study. Although the purpose of PDS I was to identify schizophrenia and other schizophrenia spectrum disorder cases, BD cases were also diagnosed by interview in that study. The protocol for the PDS I also included electronic linkages with the KPNC inpatient, outpatient, and pharmacy databases and used the same *ICD-9* diagnostic codes (295-298). Ascertainment covered the period from January 1, 1981, through December 31, 1998. The only other differences in the ascertainment and screening methods between the PDS I and the present protocol are that the PDS I did not include review of pharmacy records for treatment with mood stabilizers and included a second screening step that involved psychiatrist review of abstracted data from inpatient and outpatient records for symptoms of psychosis. The Diagnostic Interview for Genetic Studies,[11] rather than the SCID-I/P, was used to diagnose cases in the PDS I. Twenty-three BD cases were diagnosed in the PDS I. Thus, in total, 95 BD cases were diagnosed after interview and ascertainment from all sources.

After a complete description of the study to the subjects, written informed consent was obtained. The study protocol was approved by the institutional review boards of the New York State Psychiatric Institute and KPNC. The numbers of subjects ascertained, sought for interview, interviewed, and diagnosed with BD and the reasons for nonparticipation are depicted in the Figure.

Selection of Matched Controls

The first step in control selection was exclusion of CHDS cohort members with screen-positive findings for potential BD or psychotic disorders (n = 448). To ensure that controls would have been equally likely (as their matched cases) to be ascertained if they had been treated for BD in the KPNC or the ABHCS, controls were matched to cases on KPNC membership (for cases ascertained through KPNC records) or residence in Alameda County (for cases ascertained through the ABHCS or the CHDS cohort mailing) in the year the case was first treated as reported in the SCID-I/P. For the KPNC, membership in the plan at the first treatment of the case was used for control matching because cohort members would have been documented in KPNC databases if they sought care for BD. For cases treated by the ABHCS and the mailed survey, controls were ascertained using Department of Motor Vehicle records indicating residence in Alameda County at the time of case diagnosis, because these subjects represented the population at risk for treatment of BD. Most subjects who received the mailing were Alameda County residents. Potential controls enrolled in the KPNC at the time of case ascertainment were excluded from the control pool for cases identified from the ABHCS or the cohort mailing. Siblings of selected controls were excluded from further control selection, so that all controls were independent observations, each representing a single family or a single pregnant woman.

The other matching criteria included date of birth (±30 days), sex, and availability of archived maternal serum samples (for serologic studies). A maximum of an 8:1 ratio of controls to cases was achieved because the ratio represented the maximum number of controls who could be successfully matched to cases on all criteria and because it maximized statistical power.

This protocol yielded 754 matched controls. The corresponding cases and matched controls were termed a "matched set."

Description of the Analytic Sample

One family had 2 siblings with BD; one of these was excluded at random because these 2 cases represented nonindependent observations. This exclusion resulted in 94 cases. These cases consisted of 78 subjects with BD I, 12 with BD II, and 4 with BD not otherwise specified. Eight matched controls corresponding to the excluded BD case were also excluded, resulting in 746 matched controls. Two cases and 24 controls did not have influenza data, yielding 92 cases (76 with BD I, 12 with BD II, and 4 with BD not otherwise specified) and 722 matched controls for the analytic sample.

Statistical Analysis

Appropriate to the nested case-control study design, point and interval estimates of odds ratios (ORs) were obtained by fitting conditional logistic regression models for matched sets. Statistical significance was judged at $\alpha = .05$. All statistical analyses were performed using commercially available software (SAS, version 9.2; SAS Institute, Inc).

Potential confounders were identified in the literature on the basis of at least suggestive evidence in previous studies of associations with maternal infection[2] or BD.[12] These confounders included maternal age, race, educational level, and psychiatric history and gestational age at birth. Data on these factors were included in the CHDS database; all maternal variables were obtained from the gravida's self-report, whereas gestational age at birth was abstracted from obstetric/delivery records. Maternal race was defined as white (referent category), black, and other. This variable was included to assess its effects on health disparities. Maternal educational level was de-

Table 1. Demographic Characteristics and BD[a]

Characteristic	BD Cases (n = 92)	Controls (n = 722)	*P* Value
Maternal age, mean (SD), y	27.5 (6.5)	28.1 (6.0)	.37
Maternal race[b]			
White	64 (70.3)	425 (59.2)	.07
Black	22 (24.2)	207 (28.8)	
Other	5 (5.5)	86 (12.0)	
Maternal educational level			
Less than high school	18 (21.2)	121 (18.1)	.77
High school graduate	31 (36.5)	262 (39.2)	
Some college or more	36 (42.4)	286 (42.8)	
Gestational age, mean (SD), d	279.9 (14.2)	281.3 (15.9)	.35
Maternal psychiatric history			
Yes	15 (16.3)	100 (13.9)	.53
No	77 (83.7)	622 (86.1)	

Abbreviation: BD, bipolar disorder.

[a] Unless otherwise indicated, data are expressed as number (percentage) of subjects. Percentages have been rounded and might not total 100. Data were missing for maternal age for 2 subjects, maternal race for 5, and maternal educational level for 60.

[b] From categorization of ethnicities coded in the original Child Health and Development Study database. Other includes Mexican, Chinese, Japanese, Korean, American Indian, Burmese, Filipino, Hawaiian, Asian Indian, Malayan, and Siamese.

Table 2. Demographic Characteristics and Influenza Infection[a]

Characteristic	Exposed to Influenza (n = 27)	Unexposed to Influenza (n = 787)	*P* Value
Maternal age, mean (SD), y	28.2 (6.4)	28.0 (6.0)	.87
Maternal race[b]			
White	17 (63.0)	472 (60.4)	.43
Black	9 (33.3)	220 (28.1)	
Other	1 (3.7)	90 (11.5)	
Maternal educational level			
Less than high school	5 (20.8)	134 (18.4)	.61
High school graduate	7 (29.2)	286 (39.2)	
Some college or more	12 (50.0)	310 (42.5)	
Gestational age, mean (SD), d	277.0 (15.6)	280.1 (14.3)	.27
Maternal psychiatric history			
Yes	8 (29.6)	107 (13.6)	.04
No	19 (70.4)	680 (86.4)	

[a] Unless otherwise indicated, data are expressed as number (percentage) of subjects. Percentages have been rounded and might not total 100. Data were missing for maternal age for 2 subjects, maternal race for 5, and maternal educational level for 60.

[b] From categorization of ethnicities coded in the original Child Health and Development Study database. Other includes Mexican, Chinese, Japanese, Korean, American Indian, Burmese, Filipino, Hawaiian, Asian Indian, Malayan, and Siamese.

fined categorically as less than high school, high school graduate (referent category), or some college or more. Gestational age at birth was defined in days. Maternal psychiatric disorder was defined as psychoses, schizophrenia, affective disorder, anxiety, alcohol and/or substance abuse, mental deficiency, and other mental disorders. We conducted bivariate analyses to determine the association between these covariates and the outcome (BD) and influenza. In the final model, we adjusted for maternal age, race, educational level, and psychiatric history and gestational age at birth.

Results

Sample Characteristics

Among the covariates tested, only maternal race was related to BD risk, although the result fell short of statistical significance ($P = .07$) (**Table 1**). The association appeared to have been accounted for mainly by a decrease in the prevalence of BD in the category of other race. Maternal influenza exposure was significantly associated with maternal history of psychiatric disorders ($P = .04$) (**Table 2**).

Potential cases who were interviewed, compared with potential cases who were not interviewed, evidenced a trend for increased maternal age ($P = .055$) and had significantly increased gestational age at birth ($P = .03$) (**Table 3**).

Maternal Influenza and BD in Offspring

Offspring exposed to maternal influenza infection at any time during pregnancy were nearly 4 times more likely to develop BD than those who were not exposed (**Table 4**). With regard to the gestational timing of influenza, the finding was statistically significant only for the third trimester, with a nearly 5-fold increased risk of BD. A nearly 6-fold increased risk of BD was observed for influenza exposure during the second trimester, although the results did not reach statistical significance. No subject was exposed in more than 1 period of pregnancy. The findings were not appreciably altered after adjustment for maternal age, race, educational level, gestational age, and maternal psychiatric history.

Table 3. Characteristics of Potential Case Subjects Interviewed and Not Interviewed[a]

Characteristic	Potential Cases Interviewed (n = 214)	Potential Cases Not Interviewed (n = 234)	*P* Value
Maternal age, mean (SD), y	27.7 (6.7)	26.5 (6.5)	.055
Maternal race[b]			
White	119 (55.9)	118 (51.1)	.48
Black	76 (35.7)	87 (37.7)	
Other	18 (8.5)	26 (11.3)	
Maternal educational level			
Less than high school	47 (24.2)	52 (25.2)	.75
High school graduate	76 (39.2)	86 (41.7)	
Some college or more	71 (36.6)	68 (33.0)	
Gestational age, mean (SD), d	282.5 (17.7)	278.6 (19.5)	.03
Maternal psychiatric history			
Yes	21 (10.0)	25 (11.1)	.48
No	188 (90.0)	201 (88.9)	
Exposure to gestational influenza			
Exposed	13 (6.4)	13 (5.9)	.83
Unexposed	190 (93.6)	207 (94.1)	

[a] Unless otherwise indicated, data are expressed as number (percentage) of subjects. Percentages have been rounded and might not total 100. Data were missing for maternal age for 4 subjects, maternal race for 4, maternal educational level for 48, gestational age for 7, maternal psychiatric history for 13, and exposure to gestational influenza for 25.

[b] From categorization of ethnicities coded in the original Child Health and Development Study database. Other includes Mexican, Chinese, Japanese, Korean, American Indian, Burmese, Filipino, Hawaiian, Asian Indian, Malayan, and Siamese.

Table 4. Maternal Exposure to Influenza and Risk of BD in Offspring

Gestational Timing of Influenza Exposure	No. (%) of Subjects		Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)[a]	*P* Value
	Cases (n = 92)	Controls (n = 722)				
Any trimester	8 (8.7)	19 (2.6)	3.82 (1.58-9.24)	.003	4.21 (1.60-11.05)	.004
Periconceptional	1 (1.1)	4 (0.6)	2.67 (0.28-25.64)	.40	4.20 (0.38-47.06)	.25
First trimester	2 (2.2)	9 (1.2)	1.81 (0.36-9.07)	.47	2.21 (0.41-11.79)	.35
Second trimester	2 (2.2)	3 (0.4)	5.89 (0.80-43.36)	.08	7.74 (0.65-92.70)	.11
Third trimester	3 (3.3)	5 (0.7)	4.72 (1.13-19.76)	.03	5.68 (1.07-30.10)	.04

Abbreviations: BD, bipolar disorder; OR, odds ratio.

[a] Adjusted for maternal age, race, educational level, and psychiatric history and for gestational age at birth.

When the outcome was restricted to BD I, the findings were similar to the broad categorization of BD. For maternal influenza exposure during any trimester, the risk of BD I was increased more than 4-fold (OR, 4.40 [95% CI, 1.77-10.9; $P = .001$]). The ORs for specific periods of pregnancy were also very similar, at 4.00 for periconceptional exposure (95% CI, 0.36-44.1; $P = .26$), 2.43 for the first trimester (0.45-13.1; $P = .30$), 5.89 for the second trimester (0.80-43.3; $P = .08$), and 4.72 for the third trimester (1.13-19.7; $P = .03$). Maternal influenza exposure during pregnancy was also associated with an increased risk of BD with psychotic features (OR, 5.74 [95% CI, 1.52-21.7; $P = .01$]).

Given the fact that different databases were used to ascertain cases, we addressed whether the source of ascertainment affected the results. Because the cases overlapped between these sources, we conducted separate analyses of the relationship between gestational influenza during any trimester and the risk of BD in subgroups of cases defined by ever having been identified by each respective source (the KPNC and ABHCS, CHDS cohort mailing, and PDS I), regardless of whether the case was also identified by another source. We found substantially elevated and similar ORs for each of these sources (KPNC, 3.69 [95% CI, 1.05-12.99; $P = .04$]; ABHCS, 4.00 [0.94-17.0; $P = .06$]; CHDS cohort mailing, 4.00 [0.94-17.0; $P = .06$]; and PDS I, 4.00 [0.36-44.12; $P = .26$]). Although a significant association was found only for the KPNC, with statistical trends for the ABHCS and the CHDS mailing, this association was probably owing to the small number of subjects in each subgroup. In a secondary analysis of maternal respiratory infections excluding influenza, exposure during any trimester was not associated with an increased risk of BD (OR, 1.08 [95% CI, 0.67-1.76; $P = .74$]).

Discussion

The main finding of this study is that maternal influenza infection, prospectively documented during pregnancy, was associated with a nearly 4-fold increased risk of BD in adult offspring. The finding was not altered by any of the covariates tested.

Two previous studies[5,6] provided some evidence of numerical increases in maternal influenza during pregnancy in BD cases, although these studies had several limitations, as we delineated in our introduction. Methodologic strengths of the present study include prospective, physician-based diagno-

ses of influenza, use of a large birth cohort undergoing assessment for influenza before and during pregnancy and followed up for BD throughout most of the risk period for BD, structured psychiatric interviews based on standardized diagnostic criteria, and a control sample derived from the source population that gave rise to the cases. No previous study of this question included all of these design advantages, which supports the validity of the observed association.

In a previous study[1] on the CHDS birth cohort, influenza during the first half of pregnancy, documented by antibody assays in archived maternal serum specimens, was related to a 3-fold increased risk for schizophrenia and other schizophrenia spectrum disorders. The risk of BD in the present study was increased during each period of pregnancy. Although the ORs were numerically greater for the later compared with the early pregnancy periods, the interpretation of a true difference in the risk of influenza exposure between these periods is tempered by the small numbers of cases and controls within each gestational period. Nonetheless, this finding may stimulate future work aimed at testing whether the same environmental risk factor can give rise to different disorders depending on the timing of the insult. Notably, maternal viral infection in the first trimester has been associated with autism.[13,14]

Viewed more broadly, these findings may help to shed light on similarities and differences with regard to etiologic and pathogenic mechanisms of schizophrenia and BD. These illnesses are similar in several respects, including the demographic variables of sex distribution, age at onset, and population prevalence[15]; comorbidity of psychotic and mood symptoms[16]; familial aggregation[17]; susceptibility genes[18]; and response to antipsychotic medications.[19,20] However, clear differences exist between schizophrenia and BD with regard to several neuroanatomic and neuropathologic abnormalities[21,22] and neurocognitive dysfunction.[23,24] In addition, not all studies have demonstrated associations between prenatal influenza and schizophrenia, although several of these studies had significant methodologic limitations.[3]

Unlike schizophrenia, few neurobiological studies have investigated neurodevelopmental abnormalities in BD. Some studies, however, have investigated reelin, a secreted glycoprotein that regulates neuronal positioning in cortical brain structures[25] in postmortem brains of BD cases. Reelin messenger RNA expression and the number of reelin-positive cells identified by immunohistochemistry were significantly decreased by up to 50% in the prefrontal cortex of BD patients, in addition to those from schizophrenia patients, compared with controls,[26] and reelin protein levels were significantly reduced in BD cases.[27] Significant reductions in reelin-positive cell counts in neocortical and hippocampal layers were observed in mice infected prenatally with influenza,[28] and brains from juvenile mice subjected to maternal immune activation during gestation showed reduced reelin expression in the dorsal CA1 subfield of the hippocampus and diminished neurogenesis in the dentate gyrus.[29]

In a pooled analysis of T2-weighted magnetic resonance imaging findings, patients with BD were more than 3 times more likely to exhibit periventricular white matter hyperintensities compared with subjects without BD.[30] A significant excess of BD patients with deep subcortical white matter lesions were born during the winter,[31] when influenza incidence peaks[32]; although the link between periventricular white matter lesions and winter birth was statistically significant, it became nonsignificant ($P = .11$) when excess winter births in the cohort were taken into account. Nonetheless, these results are consistent with the associations in the present study.

Finally, maternal influenza exposure was significantly associated with maternal psychiatric disorders, consistent with a greater vulnerability to influenza among mothers with psychiatric disorders; this association may also provide a basis for further exploration of interactions between influenza and genetic susceptibility in BD and other psychiatric disorders. Notably, Clarke et al[33] found that maternal pyelonephritis interacted with family history of schizophrenia to increase risk of schizophrenia in offspring.

We should note some limitations of this study. First, diagnostic misclassification may have occurred. Cases of influenza in which medical attention was not sought would have been missed. Consequently, only influenza infections severe enough to be reported might have been included. In addition, because the diagnosis of an influenza infection was based on physician evaluation and not confirmed by serologic testing, diagnostic misclassification may have occurred. However, these scenarios would have most likely biased the findings toward the null because no clear reason exists for the decision to seek medical attention for influenza or for a physician's misdiagnosis of influenza to be increased for pregnant mothers of future BD cases compared with controls. Moreover, the lack of association between noninfluenza maternal respiratory infections and BD strengthens the validity of the influenza diagnosis.

Second, despite the extensive follow-up using several sources of BD cases, some cases will not be ascertained or diagnosed. Relatively early-onset cases of BD may not have been ascertained because cohort members were aged 15 to 22 years at the beginning of follow-up by the KPNC in 1981, and the mean age at onset of BD is approximately 19 to 20 years.[34] Given the age range of these cases, however, ascertainment would most likely have depended on the family's KPNC membership. Specifically, BD cases may have been lost to follow-up only if early manifestations of BD affected the family's membership in the KPNC; however, the PDS I[9] demonstrated that most of the loss to follow-up before 1981 occurred by 10 years of age, before typical manifestations of BD occur. For selection bias to have confounded the associations in this context, gestational influenza exposure and relatively early onset or early manifestations of BD would therefore need to be related to the family's KPNC membership by 1981. Although this relation is possible, these associations would need to be substantial and present in combination to have influenced our findings. With regard to the ABHCS, ascertainment began in 1993, at which time the cohort members would have been 26 to 34 years old. Cases ascertained by the ABHCS and the CHDS mailing may have a tendency for later age at onset or greater chronicity. For this possibility to have biased the findings, gestational influenza exposure would need to be related to both characteristics and to residence in Alameda County. The fact that we observed as-

sociations between gestational influenza and BD after stratifying by source of ascertainment provides evidence against selection bias. Moreover, selection bias would have been further minimized by the use of controls who represented the respective source populations for cases.

The use of the ABHCS database and CHDS mailing introduced a key advantage, namely that we were able to capture cases that included a wider spectrum of severity, a broader range of access to care, and onset at later ages than only 1 system of ascertainment. This method includes cases who left the KPNC before BD was diagnosed. Moreover, with regard to the possibility that selection bias was related to interview status, we found no differences on influenza exposure (P = .83) and several covariates between the interviewed and noninterviewed cases.

Third, the sample size was modest, particularly in the trimester-specific analyses. However, the present study contains more cases with individual-level maternal exposure information than in any previous study on this topic. Nonetheless, further studies with larger sample sizes will be necessary to confirm the present findings and to probe more precisely the specificity of timing of exposure during gestation and BD onset. Fourth, residual confounding is a possibility, mitigated to some degree by the availability of comprehensive data on potential confounders that were assessed in the study.

If influenza infection is demonstrated to be causally associated with BD in the offspring, preventative measures in pregnant women and women of child-bearing age may be warranted, particularly if other risk factors for BD are present. These measures include prepregnancy vaccination and avoidance of individuals who have overt symptoms of respiratory tract infection.

In conclusion, the findings of this study suggest that gestational infection with the influenza virus confers a nearly 4-fold increased risk of BD in adult offspring. If confirmed by studies in other birth cohorts, these findings may have implications for prevention and identification of pathogenic mechanisms that lead to BD. Further work, including serologic studies for maternal influenza antibody in archived specimens from this cohort, is warranted.

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Study concept and design: Parboosing, Schaefer, and Brown.
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