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Maternal bacterial infection during pregnancy and offspring's risk of psychoses: variation by severity of infection and offspring sex

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Abstract

Objective—Previous studies suggest that prenatal immune challenges may elevate offspring's risk of schizophrenia and related psychoses, yet there has been limited research focused on bacterial infection.

Method—This study analyzes prospectively collected data of 15,421 pregnancies enrolled between 1959 and 1966 in the study sites in Boston, Massachusetts and Providence, Rhode Island through the Collaborative Perinatal Project. The sample included 116 offspring with confirmed psychoses. We estimated associations between maternal bacterial infection during pregnancy and psychosis risk over the subsequent 40 years, stratified by offspring sex and presence of reported parental mental illness, with adjustment for covariates.

Results—Maternal bacterial infection during pregnancy was strongly associated with psychosis in offspring (adjusted odds ratio [aOR]: 1.8, 95% confidence interval [CI]: 1.2–2.7, p=0.002), which varied by severity of infection and offspring sex. The effect of multi-systemic bacterial

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infection (aOR: 2.9, 95% CI: 1.3–5.9, p_{exact}=0.01) was nearly twice the effect of less severe localized bacterial infection (aOR: 1.6, 95% CI: 1.1–2.3, p=0.03). Males were significantly more likely to develop psychosis following maternal exposure to any bacterial infection during pregnancy than females (p=0.02).

Conclusions—This study suggests that maternal bacterial infection during pregnancy is associated with an elevated risk for psychoses in offspring—an association that also varies by infection severity and offspring sex. These findings call for additional investigation and, if replicated, potentially public health and clinical efforts that focus on preventing and managing bacterial infection among pregnant women.

INTRODUCTION

Epidemiologic and preclinical studies have identified maternal viral infection during pregnancy as a putative risk factor for schizophrenia (1). However, there is a relative paucity of research on bacterial infection (2–4). Bacterial infections—such as urinary tract infection and bacterial vaginosis—are highly prevalent as a result of physiological changes and immune suppression during pregnancy (5). Often asymptomatic, bacterial infections are largely overlooked and left untreated in antenatal care settings. However, such infections can pose a significant threat to pregnancy and healthy fetal development (6,7). Further, if untreated, they have been associated with severe neurodevelopmental disorders in offspring (8,9).

Despite considerable evidence on the immediate impact of gestational bacterial infection on perinatal health, long-term neuropsychiatric consequences remain unclear. There have been only two prior prospective cohort studies that specifically investigated bacterial infection in relation to offspring's risk for psychoses. One study reported that maternal sinusitis, tonsillitis, pneumonia, cystitis, pyelonephritis, or bacterial venereal infection was associated with a more than 2-fold increase in schizophrenia risk (2). This was replicated in another study specific to pyelonephritis (10). We previously reported that maternal immune dysregulation in general was associated with significantly higher risk of offspring psychoses (11,12), although this was not specifically tied to bacterial infection.

Animal studies have provided robust experimental evidence explaining how maternal bacterial infection during pregnancy may cause lasting changes in the structure and function of the fetal brain (13,14). For example, murine embryos exposed to the bacterial cell wall exhibited abnormal proliferation of neuronal precursor cells, permanently altering their brain architecture (15). After birth, exposed offspring displayed behavioral, neurochemical and neurophysiologic abnormalities consistent with observations in people with psychotic illness (15). Taken together, these experimental studies provide a strong rationale to test the hypothesis that maternal bacterial infection during pregnancy disrupts fetal neurodevelopment consistent with subsequent risk for psychoses using epidemiologic samples. Thus, we hypothesized that maternal bacterial infection during pregnancy increases offspring's risk of psychoses in adulthood, and that the magnitude of this association varies as a function of severity of infectious exposure.

Earlier studies, including by our group, reported associations between gestational immune disruption and heightened risk of psychoses among males to a greater extent than females (12,16–18). To replicate these findings, we hypothesized that the effect of maternal bacterial infection during pregnancy on the risk of psychoses would be greater among male than female offspring. In addition to sex differences, numerous studies have reported on strong heritability of psychotic illnesses (19), with a substantial overlap with other psychiatric disorders (20). In fact, previous studies have demonstrated the utility of family history as a proxy of genetic liability (19,21), and one of them has specifically investigated synergistic effects of familial liability to psychosis and prenatal bacterial infection on subsequent risk for schizophrenia (10). These findings were substantiated by a more recent study that the impact of parental history of mental disorder was not confined to concordant parental mental disorders but rather offspring are at increased risk of a wide range of mental disorders (20). Taken together, we hypothesized that the association between maternal bacterial infection during pregnancy and psychosis risk would be greater among offspring with parental history of mental illness than among those without.

METHODS

Study Population

There were 16,188 live births enrolled between 1959 and 1966 at the Boston and Providence sites of the Collaborative Perinatal Project (CPP), currently known as the New England Family study (NEFS). The CPP was initiated over 50 years ago to investigate prospectively the prenatal and familial antecedents of pediatric, neurological, and psychological disorders of childhood (22). Details of the CPP and NEFS methodology are reported in previous publications (11,23–26). As shown in Figure 1, we excluded offspring who did not survive to the period of risk for psychosis (n=467), who had entirely missing record for infectious disease during pregnancy (n=44), who had prenatal infection of unknown etiology (n=156). In a series of previous follow-up studies of the NEFS participants, we identified those with psychoses among the original parents and offspring, now adults in their 50s (11,23–26). To minimize false positive cases of psychoses in offspring, we further excluded those who had a treatment history for organic or substance-induced psychoses (n=100). The final analytic sample included a total number of 15,421 participants.

Collection and Processing of the Exposure Data

Collection of the exposure data were jointly conducted by trained non-physician interviewers and physicians beginning at the time of registration for prenatal care at intervals of four weeks during the first 7 months of pregnancy, every two weeks at 8 months, and every week thereafter, using standardized protocols, forms, manuals, and codes (26). Throughout the initial and repeat prenatal visits, interviewers were responsible to collect of reproductive and gynecological history, recent and past medical history, and family health and genetic history. They were also responsible to conduct infectious disease and system review at the initial visit or as soon thereafter as possible. Physicians were responsible to review the data collected by the interviewer, collect further details on past and recent medical history, complete initial prenatal examination and observations, and record the date and list any diagnoses unrelated to prenatal care that comes to his or her attention. Medical

and lay editing was subsequently carried out in conjunction with participant's complete hospital records by the obstetric coordinator or a board-qualified obstetrician. Lastly, the entire study record was summarized together with complete hospital record no later than 6 months after termination of a given pregnancy.

Ascertainment of Exposure Status

The primary exposure variable included any bacterial infections that occurred during pregnancy, defined as the time period between the estimated date of conception and the end of the third stage of labor. If women had more than one infection, they were counted only once using the Boolean OR operator. Infections that pertained to more than one major organ system were defined as multi-systemic infections (e.g., sepsis), whereas those specifically affecting one system (e.g., vaginitis) were defined as localized infections. There were a total of 399 multi-systemic and 3,201 localized infections during pregnancy. Localized bacterial infections included: tuberculosis (n=8), pneumonia (n=83), syphilis (n=66), gonorrhea (n=15), kidney, ureter, and bladder (KUB) infection (n=1,203), and vaginitis (n=2,136).

Assessment of Offspring with Schizophrenia and Related Psychoses

Cohort members with psychosis were identified between the ages of 32 and 39 through a systematic follow-up of the entire New England cohorts of the CPP from 1997 to 2003. The parents and offspring with history of psychiatric hospitalization and/or possible psychotic and bipolar illness were identified from the following sources: (a) record linkages with public hospitals, mental health clinics, and the Massachusetts and Rhode Island Departments of Mental Health; (b) several follow-up and case-control studies nested within the larger New England cohort involving direct interviews; (c) reports from participants in these interview studies of family members with a history of psychotic or bipolar symptoms or diagnosis. Adult offspring with major psychoses within the New England cohorts were identified through a 2-stage diagnostic assessment procedure from 1996 to 2007, approximately 30 years after and blind to prior assessments. In stage 1, 249 individuals with possible psychotic illness were identified through systematic follow-up and subsequently diagnosed through administration of the Structured Clinical Interview for DSM-IV Axis I Disorders (27) (n=173) or review of medical charts alone (n=76). Based on interview data and medical record review, trained PhD- and MD-level diagnosticians then completed best-estimate consensus diagnoses according to DSM-IV criteria for life time prevalence of psychotic and other psychiatric disorder (28). A total of 116 adult offspring were determined to have a non-organic psychotic disorder including schizophrenia disorders (n=52; schizophrenia, schizoaffective depressed type), affective psychoses (n=53; schizoaffective bipolar, bipolar with psychotic features, major depressive disorder with psychosis), and other non-affective psychoses (n=11; delusional disorder, brief psychosis, non-affective psychoses type not specified) (11). Human subject's approval was granted by institutional review boards at Harvard University, Brown University, and local psychiatric facilities. Written consent was obtained from all interviewed subjects, and they were compensated for their participation.

Covariates

Covariates included maternal race/ethnicity, study site, years of maternal education, parental socioeconomic index, and year and season of birth. A socioeconomic index, which as adapted from the Bureau of the Census and derived from the education and occupation of the head of household along with household income was assigned to each pregnancy; this continuous measure was later categorized based on quartiles (29). We further adjusted for reported parental history of mental illness (when we did not test for its effect modification) as a known risk factor for schizophrenia (20) that has also been found to be associated with infections (30). Previously, our group has reported that psychiatric history of both parents may independently predict offspring's risk for psychoses (31). In this study, we operationalized genetic susceptibility to psychiatric disorder by aggregating the information collected from the mothers about their own as well as their spouse's history of nervous problem requiring hospitalization, psychiatric treatment, or other therapy (i.e., clinically significant nervous problem) at two timepoints: during pregnancy and the offspring's age 7 visit. The overall rate of reported parental history of mental illness was 11%. Additionally, we adjusted for maternal exposure to viral infection during pregnancy to address potential confounding by concomitant viral infection. Lastly, we controlled for offspring's participation in the final follow-up of the larger CPP study—conducted at offspring's age of 7—given its strong relationship with the likelihood of being identified as a psychotic case in adulthood.

Statistical Analyses

We used Chi-square and *t*-tests (2-sided) to compare the demographic and perinatal characteristics of: (a) the exposed and unexposed mothers, and (b) the cases and non-cases. Logistic regression analyses were used to estimate odds ratios of psychoses for maternal exposure to any and localized bacterial infections during pregnancy. Logistic regression models were adjusted for maternal neurologic/psychiatric conditions during pregnancy, maternal education, socioeconomic index, maternal race/ethnicity, study site, season and year of birth, parental history of mental illness, participation in the final follow-up of the larger CPP study, and concomitant viral infection during pregnancy. Exact logistic regression analyses were used to estimate the effects of multi-systemic bacterial infection given the small number of cases exposed to this type of infection. In these models, we could only adjust for few covariates that are reported to be key confounders in the hypothesized relationship and had strong statistical associations with both the exposure and outcome in the analytic sample (see Tables 1 and 2). Lastly, we examined effect modification of the hypothesized associations by offspring sex alone and presence of parental mental illness alone using Wald statistics. All analyses were conducted using SAS version 9.4 (32).

Sensitivity Analyses

Given that instances of maternal bacterial infection during pregnancy were not all serologically confirmed, some may have been misclassified (i.e., false positive). If a reported instance of bacterial infection was accompanied by any antibacterial treatment (e.g., chloramphenicol, erythromycin, furadantin, penicillin, streptomycin, tetracycline) and/or a physician's diagnosis, we defined this as confirmed and conducted analyses considering

only confirmed instances of bacterial infection. Out of 15,421 cohort mothers included in the analytic sample, 15,327 (99.4%) had at least one of these two sources of information available to confirm their exposure status. We assessed the robustness of our findings to potential misclassification of exposure by replicating the main effects (reported in Table 3) with the confirmed instances of bacterial infection.

RESULTS

Descriptive Results

Mothers who had bacterial infections during pregnancy were more likely to be non-white, non-married, younger, less educated, have lower socioeconomic status, reside in Providence, have neurologic-psychiatric conditions during pregnancy, and report their own or their spouse's history of clinically significant nervous problems compared to mothers who had no bacterial infection during pregnancy (see Table 1).

When examined with respect to psychosis status in adulthood, cases were more likely to have at least one parent with a clinically significant mental illness and to have participated in the study at the age of 7 than non-cases (see Table 2). Mothers of cases were more likely to be nonwhite, reside in Providence, have neurologic-psychiatric conditions during pregnancy, and be less educated than mothers of non-cases.

Main Results

Out of 15,421 cohort mothers in the analytic sample, 3,499 (23%) of them had bacterial infection; 399 (3%) had systemic infection, 3,191 (21%) had localized infections, and 91 (<1%) had both. As depicted in Table 3, maternal bacterial infection during pregnancy was significantly associated with psychotic illnesses among adult offspring (adjusted odds ratio [aOR]: 1.8, 95% confidence interval [CI]: 1.2–2.7). Multi-systemic bacterial infection was more strongly associated with later development of psychosis (aOR: 2.9, 95% CI: 1.3–5.9) than localized bacterial infection (aOR: 1.6, 95% CI: 1.1–2.3).

As shown in Table 4, the association between prenatal exposure to any bacterial infection and subsequent psychosis was significantly modified by offspring sex. Males offspring were nearly three times more likely to develop psychoses following maternal bacterial infection during pregnancy whereas female offspring showed no difference in the likelihood by the exposure status (males: aOR: 2.6, 95% CI: 1.6–4.2; females: aOR: 1.0, 95% CI: 0.5–1.9; p=0.018). Similarly, males were more than twice as likely to develop psychoses compared to females following maternal exposure to localized bacterial infection (males: aOR: 2.1, 95% CI: 1.2–3.4; females: aOR: 1.0, 95% CI: 0.5–1.9; p=0.084). Since there was only one female case exposed to multi-systemic bacterial infection, we reported results specific to males without evaluating statistical significance of effect modification. Males who were prenatally exposed to multisystemic infection had five times the odds of developing psychoses relative to unexposed males (aOR: 5.0, 95% CI: 2.0–10.7).

As presented in Table 5, we observed somewhat greater magnitude of hypothesized associations among offspring with reported parental mental illness compared to those without but with no statistical support for effect modification.

Sensitivity Analyses

Of the 3,499 reported instances of bacterial infection, 1,785 (51%) were confirmed based upon treatment with antibiotics and/or medical diagnosis. Of the 399 reported instances of multi-systemic bacterial infection, 357 (89%) were confirmed. Of the 3,191 instances of localized bacterial infection, 1,513 (47%) were confirmed. Using the confirmed instances of bacterial infection, we were able to replicate the same patterns of associations from the main analyses. As expected, the magnitude of the hypothesized associations was slightly increased in the sensitivity analyses—potentially due to the reduction of nondifferential misclassification of exposure (see Online Supplementary Tables 1–3).

DISCUSSION

Maternal bacterial infection during pregnancy was significantly associated with subsequent development of schizophrenia and related psychoses among offspring. While localized bacterial infection predicted a 1.6-fold increase in the odds of developing psychoses in adulthood, multi-systemic bacterial infection predicted a nearly 3-fold increase in the odds. Furthermore, maternal bacterial infection was more strongly associated with the likelihood of developing psychosis among male than female offspring and this effect modification was statistically significant for any bacterial infection (p=0.018) and nearly significant for localized bacterial infection (p=0.084). However, these findings need to be interpreted with caution given the overlapping confidence intervals of sex-specific estimates. In addition, we found no statistical evidence for the hypothesized effect modification by reported parental mental illness, possibly because our measure of parental mental illness is a limited indicator of genetic risk.

Findings in this study underscore the potential role of maternal bacterial infection during pregnancy in the etiology of psychotic disorders. Maternal bacterial infection during pregnancy has been found to induce the production of cytokines by the maternal immune system, placenta, or the fetus itself (33). Our group and others found significant associations of prenatal levels of pro-inflammatory cytokines with offspring's risk of schizophrenia and related psychoses (11,34,35) which, in a direct test, differed by sex (11). Others suggested that the effects of bacterial infection may not be specific to the prenatal period but that these findings implicate a generally increased familial susceptibility to infections—both during and outside pregnancy (36). Although we cannot test this hypothesis with the CPP, future studies may examine the effects of bacterial infection occurring before, during, and after pregnancy and ascertain their temporal specificity on psychosis risk.

Sex Difference in Schizophrenia and Related Psychoses

Our findings suggest that maternal bacterial infection during pregnancy may differentially affect the development of schizophrenia and related psychoses dependent on offspring sex. This is consistent with the long history from our group (11,37,38) and from others (39) investigating sex differences in psychoses relating disease risk, course, and outcome. Some have suggested the role of the placenta, in that the placenta of females may possess greater ability to adapt to fluctuating *in utero* environmental conditions (such as prenatal immune challenges) compared with that of males (40). However, the mechanisms underlying a male-

specific vulnerability remain uncertain. Perhaps these effects could be due to reduced maternal-fetal compatibility for male fetuses which may need to up-regulate immune-associated transcripts to resist an attack by the maternal immune system (41). In a study of healthy fetuses, males had higher levels of cytokines indicative of a Th1-type (i.e., pro-inflammatory) response and expression of genes involved in the immune system and inflammation (42). In contrast, females had higher levels of cytokines indicative of Th2-type (i.e., anti-inflammatory) response and expression of genes involved in immune regulation. Upon stimulation with bacterial endotoxin, levels of IL-1 and IL-6 were significantly higher in male fetal blood samples than in female fetal blood samples (43), consistent with our previous findings in maternal sera related to psychosis risk in males (11). Given that these pro-inflammatory cytokines have long been implicated in schizophrenia and related psychoses, these findings further elucidate a potential pathway explaining male vulnerability to psychoses with regard to maternal bacterial infection during pregnancy.

Strengths and Limitations

The major strength of this study is that reports of bacterial infection were obtained during pregnancy, and clinical diagnoses of schizophrenia and related psychoses among offspring were systematically gathered based on chart diagnoses and in-person structured interviews with participants, allowing us to investigate prospective relationships between maternal bacterial infection during pregnancy and offspring's risk of psychoses.

Our study also had some limitations. The first limitation is related to case identification procedures in the current study and the resulting case series. The 116 cases (0.7% of cohort) may not include all instances of schizophrenia and related psychoses among this cohort. In fact, our group was primarily seeking to enroll the most severe cases of psychoses and the anticipated prevalence of this subset of psychoses was 2.4% (44). In the study design phase, we excluded those who had organic or substance-induced psychosis to minimize false positive cases of psychoses. In the analytic phase, we adjusted all statistical models for the effect of participation in the final follow-up assessment of the larger CPP study at offspring's age of seven—which was a strong predictor of being identified as a psychotic case in adulthood. Based on our previous examination of study participants, we conclude that this likely impacts the statistical power, but would not expect the completeness of ascertainment to differ in relation to prenatal infections. Owing to the limited power, we were not able to formally test effect modification for multi-systemic bacterial infection and determine whether the findings are specific to schizophrenia, non-affective psychosis, or other classes of psychoses.

Nevertheless, it is important to note that cases identified through our record linkages with tertiary public hospitals tend to over-represent persons with greater severity of conditions, and lower socioeconomic status, and under-represent high-functioning cases without hospitalization. In contrast, cases identified through our direct follow-up and interview studies tend to over-represent those with greater residential stability, levels of independent functioning, and socioeconomic status as described in our earlier publication (45). Given our use of various methods of case ascertainment, we do not expect extreme bias towards persons of higher or lower severity as both poles of psychosis severity spectrum may have

been slightly over-represented in the current study. Based on our group's previous analyses of the considerable amount of information available from this longitudinal study (12), it does not seem that the ascertained cases differ considerably from expectations, for instance in terms of gender distribution, socio-economic level or family history of mental illness.

Another limitation pertains to the potential misclassification of exposure. Most previous studies have determined maternal bacterial infection during pregnancy based on maternal self-reports or clinical records (2–4). Similarly, we also used clinical records as the primary source of exposure information. Since the most prevalent types of bacterial infection are often asymptomatic, it is likely that some occurrences were not recorded and/or more severe instances were included (8). Several population-based studies have employed antibiotic use as a proxy of bacterial infection (46). They demonstrated that a focus on antibiotic prescription and utilization allows for an ascertainment of a wide range of bacterial infections with different severity and potentially reduces false negatives. Inspired by this approach, we identified a subset of reported instances of bacterial infection that had corresponding medical diagnosis and/or treatment history with antibacterial medications and conducted sensitivity analyses. Possibly due to the reduction of non-differential misclassification of exposure, the estimated effects of prenatal bacterial infection from the sensitivity analyses were slightly greater in magnitude than those from the main analyses.

Lastly, it is essential to note the possibility of other mechanisms that may interact with the biological mechanism that was examined in the current study. In our analytic sample, prenatal bacterial infection was associated with several socioeconomic covariates, highlighting the importance of social factors in determining the occurrence of exposure. In fact, our group has previously reported that socioeconomic disadvantages during pregnancy —measured by parental education, income, occupation, and family structure—may significantly increase the risk for neurological abnormalities in offspring (47). In the subsequent study, we reported that this association could be partially explained by socioeconomically driven variations in gestational immune activity—which was quantified using archived maternal sera collected during pregnancy (48). In future studies, we may investigate the joint contribution of bacterial infection and socioeconomic disadvantage during pregnancy and potentially delineate a more comprehensive etiologic mechanism for schizophrenia and related psychoses.

CONCLUSION

There is considerable evidence that gestational viral infections during pregnancy have adverse consequences in offspring (1). Our study was consistent with this and extended previous work by demonstrating significant impact of maternal bacterial infection during pregnancy on later risk for schizophrenia and related psychoses, which was particularly dependent on the severity of infection and offspring sex. These findings could be an important first step to motivating large-scale national register investigation of this type of research question. Larger samples would provide opportunities to address some of the crucial components on the etiologic pathway from prenatal bacterial infection and psychosis, such as gestational timing of exposure, sex-specific transmission of psychotic illness, specific subtypes of psychosis, and finer categorization of infectious exposure. If replicated,

they would also call for public health and clinical efforts that focus on preventing and managing bacterial infection among pregnant women. It is crucial to evaluate both short- and long-term consequences associated with different types of bacterial infection and antibacterial medication to avoid untoward effects on the mother and fetus (15,49).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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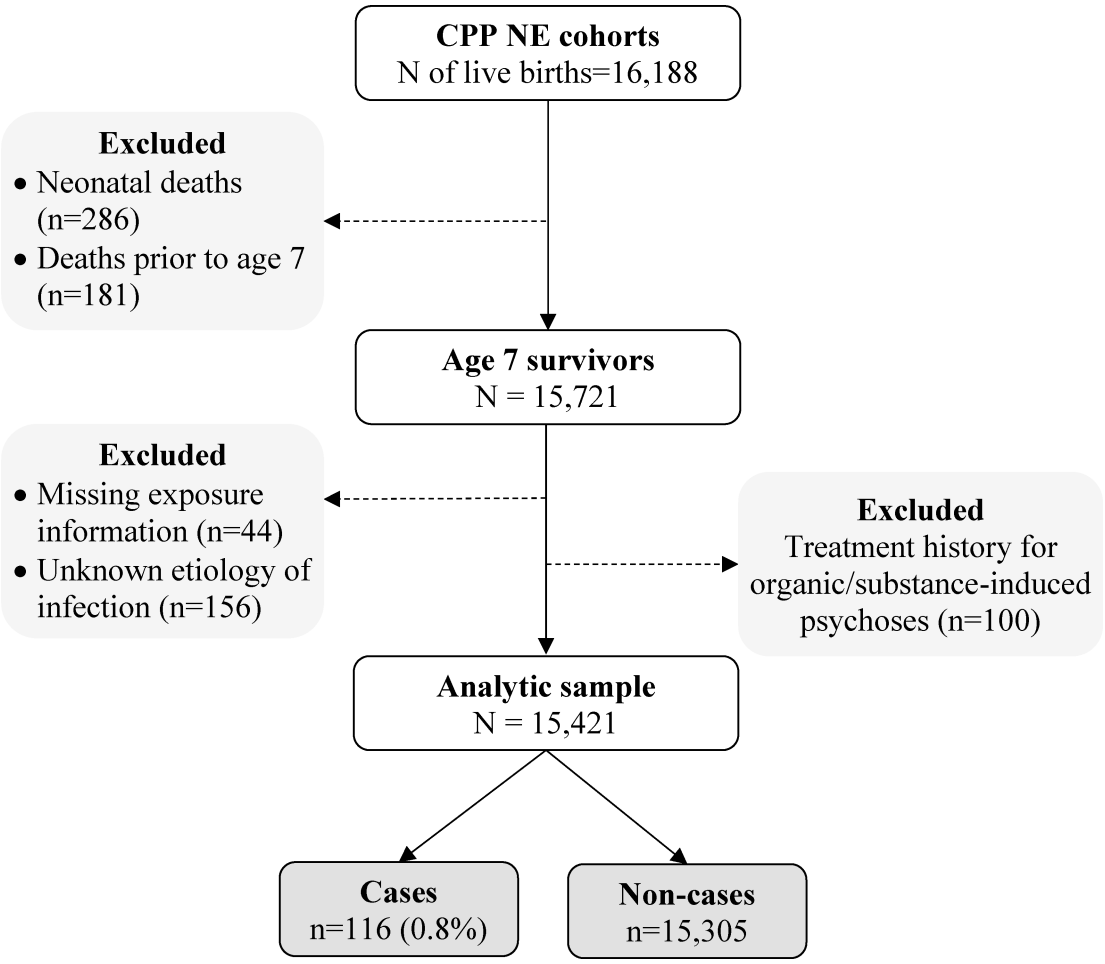

Figure 1.
Selection of analytic sample from the New England (NE) cohorts of the Collaborative Perinatal Project (CPP).

Table 1.

Descriptive statistics by maternal bacterial infection during pregnancy.

	Exposed		Unexposed		
Characteristics	**N**	**%**	**N**	**%**	***P***
Total	3,499	22.7	11,922	77.3	
Offspring sex					0.52
Male	1,755	22.3	6,101	77.7	
Female	1,743	23.0	5,819	77.0	
Maternal race/ethnicity					<0.0001
White	2,931	22.0	10,365	78.0	
Non-white	568	26.7	1,557	73.3	
Maternal marital status					<0.0001
Married	3,015	21.9	10,755	78.1	
Non-married	484	29.4	1,165	70.6	
Maternal neurologic-psychiatric conditions during pregnancy[a]					<0.0001
Present	619	28.7	1,541	71.3	
Not present	2,859	23.7	9,197	76.3	
Parental history of mental illness					<0.0001
Present	480	27.5	1,266	72.5	
Not present	2,964	22.1	10,410	77.9	
Season of birth					0.92
Spring	856	22.6	2,927	77.4	
Summer/Fall/Winter	2,955	22.7	8,995	77.3	
Study site					0.0012
Boston	2,576	22.1	9,096	77.9	
Providence	923	24.6	2,826	75.4	
Participation in the final follow-up of the Collaborative Perinatal Project study					0.44
Yes	2,714	22.8	9,173	77.2	
No	785	22.2	2,749	77.8	
Socioeconomic index					<0.0001
1st quartile (Lowest)	1,033	25.4	3,027	74.6	
2nd quartile	967	23.7	3,089	76.3	
3rd quartile	731	21.7	2,635	78.3	
4th quartile (Highest)	670	19.9	2,697	80.1	
Viral infection during pregnancy					0.10
Present	238	24.8	721	75.2	
Not present	3,291	22.6	11,201	77.4	
	Mean	**SD**	**Mean**	**SD**	***P***
Maternal age	24.9	5.9	25.2	5.9	0.017
Years of maternal education	11.1	2.5	11.4	2.5	<0.0001
Year of birth	1962.8	1.9	1962.6	1.9	<0.0001

Number and proportion of missing observations: offspring sex, n=3 (0.02%); maternal marital status, n=2 (0.02%); maternal neurologic-psychiatric conditions during pregnancy, n=1,205 (7.8%); parental history of mental illness, n=310 (2.0%); socioeconomic index, n=584 (3.8%); year of birth, n=7 (0.05%). We created a separate category for these missing data and ensured that they were included in the analytic sample.

[a]Maternal neuro-psychiatric conditions during pregnancy included convulsive disorder (not eclamptic), convulsions (not eclamptic), had mental retardation, organic brain disease, psychosis/neurosis, other neurologic or neuromuscular disease (including brain surgery), drug habituation/addiction, and alcoholism.

Table 2.

Descriptive statistics by clinical diagnosis of adult psychoses in offspring.

	Psychotic		Non-psychotic		
Characteristics	**N**	**%**	**N**	**%**	***P***
Total	116	0.8	15305	99.2	
Offspring sex					0.25
Male	68	0.9	7,788	99.1	
Female	48	0.6	7,514	99.4	
Maternal race/ethnicity					0.0029
White	89	0.7	13,207	99.3	
Non-white	27	1.3	2,098	98.7	
Maternal marital status					0.98
Married	104	0.8	13,666	99.2	
Non-married	12	0.7	1,637	99.3	
Maternal neurologic-psychiatric conditions during pregnancy[a]					0.017
Present	26	1.2	2,134	98.8	
Not present	85	0.7	11,971	99.3	
Parental history of mental illness					<0.001
Present	27	1.6	1,719	98.4	
Not present	88	0.7	13,277	99.3	
Season of birth					0.75
Spring	27	0.7	3,756	99.3	
Summer/Fall/Winter	89	0.8	11,549	99.2	
Study site					0.033
Boston	78	0.7	11,594	99.3	
Providence	38	1.0	3,711	99.0	
Participation in the final follow-up of the Collaborative Perinatal Project study					0.010
Yes	101	0.9	11,786	99.1	
No	15	0.4	3,519	99.6	
Socioeconomic index					0.063
1st quartile (Lowest)	33	0.8	4,027	99.2	
2nd quartile	37	0.9	4,009	99.1	
3rd quartile	30	0.9	3,336	99.1	
4th quartile (Highest)	14	0.4	3,351	99.6	
Viral infection during pregnancy					0.93
Present	7	0.7	952	99.3	
Not present	109	0.8	14,353	99.2	
	Mean	**SD**	**Mean**	**SD**	***P***
Maternal age	25.2	5.9	25.1	5.9	0.83
Years of maternal education	10.7	2.0	11.4	2.5	0.0029
Year of birth	1962.4	2.0	1962.7	1.9	0.10

Number and proportion of missing observations: offspring sex, n=3 (0.02%); maternal marital status, n=2 (0.02%); maternal neurologic-psychiatric conditions during pregnancy, n=1,205 (7.8%); parental history of mental illness, n=310 (2.0%); socioeconomic index, n=584 (3.8%); year of birth, n=7 (0.05%). We created a separate category for these missing data and ensured that they were included in the analytic sample.

[a]Maternal neuro-psychiatric conditions during pregnancy included convulsive disorder (not eclamptic), convulsions (not eclamptic), had mental retardation, organic brain disease, psychosis/neurosis, other neurologic or neuromuscular disease (including brain surgery), drug habituation/addiction, and alcoholism.

Table 3.

Associations between maternal bacterial infection during pregnancy and offspring's risk for schizophrenia and related psychoses in adulthood.

		Unadjusted			Adjusted		
Exposure type	**n_{case}***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Any bacterial infection	43	2.0	1.4–3.0	<0.001	1.8[a]	1.2–2.7	0.002
Localized bacterial infection	36	1.7	1.1–2.5	0.012	1.6[a]	1.1–2.3	0.027
Multi-systemic bacterial infection	9	3.2[b]	1.4–6.4	0.006	2.9[b,c]	1.3–5.9	0.011

Abbreviations: OR odds ratio; CI: confidence interval.

*Number of psychotic cases exposed to a given type of bacterial infection during pregnancy.

[a]Odds ratio were adjusted for maternal education, socioeconomic index, maternal race/ethnicity, maternal neurologic/psychiatric conditions during pregnancy, study site, season and year of birth, offspring sex, parental history of mental illness, participation in the final follow-up of the Collaborative Perinatal Project study, and viral infection during pregnancy through multivariate logistic regression models.

[b]We fitted exact logistic regression for multi-systemic bacterial infection and estimated exact p-values.

[c]Odds ratio was adjusted for viral infection during pregnancy, parental history of mental illness, and maternal race/ethnicity.

Table 4.

Stratified analyses by offspring sex for the hypothesized associations.

			Unadjusted			Adjusted		
Exposure type	**Offspring sex**	**n_{case}***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Any bacterial infection	Male	31	2.9	1.8–4.8	0.019	2.6[a]	1.6–4.2	0.018
	Female	25	1.1	0.6–2.1		1.0[a]	0.5–1.9	
Localized bacterial infection	Male	8	2.2	1.4–3.7	0.085	2.1[a]	1.2–3.4	0.084
	Female	12	1.1	0.5–2.1		1.0[a]	0.5–1.9	
Multi-systemic bacterial infection	Male	11	5.3[b]	2.2–11.3	-	5.0[b,c]	2.0–10.7	-
	Female	1	-	-		-	-	

Abbreviations: OR odds ratio; CI: confidence interval.

*Number of psychotic cases exposed to a given type of bacterial infection during pregnancy.

[a]Odds ratios were adjusted for maternal education, socioeconomic index, maternal race/ethnicity, study site, season and year of birth, parental history of mental illness, participation in the final follow-up of the Collaborative Perinatal Project study, maternal neurologic/psychiatric conditions during pregnancy, and viral infection during pregnancy through multivariate logistic regression models.

[b]We fitted exact logistic regression among male participants given the limited number of female cases exposed to multi-systemic bacterial infection. Accordingly, the interaction term was not tested for statistical significance for this type of bacterial infection.

[c]Odds ratios and confidence intervals were adjusted for viral infection during pregnancy, parental mental illness, and maternal race/ethnicity.

Table 5.

Stratified analyses by parental history of mental illness for the hypothesized associations.

			Unadjusted			Adjusted		
Exposure type	**PMI**	**n_{case}***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Any bacterial infection	Present	13	2.5	1.2–5.3	0.73	2.3[a]	1.1–5.0	0.42
	Not present	29	1.7	1.1–2.7		1.6[a]	1.0–2.6	
Localized bacterial infection	Present	11	2.1	1.0–4.6	0.41	2.0[a]	0.9–4.5	0.41
	Not present	24	1.4	0.9–2.3		1.4[a]	0.9–2.2	
Multi-systemic bacterial infection	Present	4	4.5[b]	1.5–13.4	0.63	4.6[b,c]	1.5–13.8	0.58
	Not present	5	2.4[b]	1.0–6.0		2.4[b,c]	1.0–5.9	

Abbreviations: PMI, parental history of mental illness; OR odds ratio; CI: confidence interval.

*Number of psychotic cases exposed to a given type of bacterial infection during pregnancy.

[a]Odds ratios were adjusted for maternal education, socioeconomic index, maternal race/ethnicity, study site, season and year of birth, offspring sex, participation in the final follow-up of the Collaborative Perinatal Project study, maternal neurologic/psychiatric conditions during pregnancy, and viral infection during pregnancy through multivariate logistic regression models.

[b]We fitted exact logistic regression for multi-systemic bacterial infection and estimated exact p-values.

[c]Odds ratios and confidence intervals were adjusted for viral infection during pregnancy, offspring sex, and maternal race/ethnicity.