Brown University

The Neurodevelopmental Impact of Prenatal Bacterial Infection on Adult Psychosis: Evidence from the New England Family Study

By Heather Young-A Lee

B.A., New York University, 2014

A dissertation submitted in partial fulfillment of the requirements of the Degree of Doctor of Philosophy in Epidemiology in the Brown University Graduate School and Brown University School of Public Health, Department of Epidemiology

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dissertation requirement for the degree of Doctor of Philosophy.

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[1] Lee Y, Papandonatos GD, Savitz DA, Heindel, WC, Buka SL. Effects of Prenatal Bacterial Infection on Cognitive Performance in Early Childhood: Joint Inverse Probability Weighted Adjustment for Treatment and Censoring. *Submitted to Epidemiology.* 2019.

[2] Lee Y, Cherkerzian S, Seidman LJ, Papandonatos GD, Savitz DA, Tsuang MT, Goldstein JM, Buka SL. Maternal bacterial infection during pregnancy and offspring's risk of psychoses: variation by severity of infection and offspring sex. *Under revision at American Journal of Psychiatry*. 2019.

[3] Hankerson SH, Lee Y, Brawley DK, Braswell K, Wickramaratne PJ, Weissman MM. Screening for Depression in African-American Churches. *American Journal of Preventive Medicine*. 2015; 49(4): 526–533.

[4] Szpiro S, Lee Y, Wright B, Carrasco-Queijeiro M. Alternating training between tasks enables visual perceptual learning. *Journal of Vision*. 2013; 13:249.

PRESENTATIONS

[1] Lee Y, The Neurodevelopmental impact of prenatal bacterial infection on adult psychosis: evidence from the Collaborative Perinatal Project. Talk presented at *The 109th Annual Meeting of the American Psychopathological Association*, New York, NY, Mar 2019.

[2] Lee Y, Papandonatos GD, Savitz DA, Heindel, WC, Buka SL. Effects of Prenatal Bacterial Infection on Cognitive Performance in Early Childhood. Poster presented at *The 109th Annual Meeting of the American Psychopathological Association*, New York, NY, Mar 2019.

[3] Lee Y, Gilman SE, Buka SL. Prenatal bacterial Infection and chronicity and severity of depression in adulthood. Poster presented at *Public Health Research Day*, Providence, RI, Apr 2018.

[4] Lee Y, Gilman SE, Buka SL. Prenatal bacterial Infection and chronicity and severity of depression in adulthood. Poster presented at *The 21st Annual Mind Brain Research Day*, Providence, RI, Mar 2018.

[5] Lee Y, Goldstein JM, Seidman LJ, Tsuang MT, Buka SL. Prenatal infections and risk for autism spectrum disorder: new diagnostic classification using the Collaborative Perinatal Project. Poster presented at *The 108th Annual Meeting of the American Psychopathological Association*, New York, NY, Mar 2018.

[6] Lee Y, Goldstein JM, Seidman LJ, Tsuang MT, Buka SL. Prenatal bacterial Infection and adult psychosis: variation by sex and parental mental illness. Poster presented at *The 108th Annual Meeting of the American Psychopathological Association*, New York, NY, Mar 2018.

[7] Lee Y, Goldstein JM, Seidman LJ, Tsuang MT, Buka SL. Prenatal exposure to bacterial infection and risk for schizophrenia and other psychoses. Poster presented at *Public Health Research Day*, Providence, RI, Apr 2017.

[8] Lee Y, Goldstein JM, Seidman LJ, Tsuang MT, Buka SL. Maternal exposure to bacterial infections during pregnancy and risk for schizophrenia and other psychoses among adult offspring. Poster presented at *The 107th Annual Meeting of the American Psychopathological Association*, New York, NY, Mar 2017.

[9] Lee Y, Shrout PE. The impact of religion on mental health service use: results from National Survey of American Life (NSAL). Poster presented at *The 16th Annual Convention of the Society for Personality and Social Psychology*, Long Beach, CA, Feb 2015.

[10] Lee Y, Shrout PE. Religious participation and mental health service use in depressed African Americans. Poster presented at *The 40th Annual Undergraduate Research Conference*, New York, New York, Mar 2014.

[11] Lee Y, Szpiro S, Wright BA, Carrasco-Queijeiro M. Alternating training between tasks enables visual perceptual learning. Poster presented at *The Columbia University Spring Undergraduate Research Symposium*, New York, NY, Mar 2013.

[12] Lee Y, Szpiro S, Wright BA, Carrasco-Queijeiro M. Alternating training between tasks enables visual perceptual learning. Poster presented at *The 39th Annual Undergraduate Research Conference*, New York, NY, May 2013.

[13] Lee Y, Szpiro S, Wright BA, Carrasco-Queijeiro M. Alternating training with another task enables visual perceptual learning. Poster presented at *The 13th Annual Stanford University Undergraduate Psychology Conference*, Stanford, California, May 2013.

SKILLS

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RESEARCH INTERESTS

Substantive:

- Identification of infectious and immune biomarkers associated with clinical dysfunctions of neurodevelopmental disorders
- Intergenerational transmission of major psychiatric disorders; interaction between environmental and genetic susceptibility.

Methodological:

- Causal inference methods
- Survey data analysis
- Longitudinal data analysis
- Predictive modeling in mental health

Preface

This dissertation takes the form of three publishable manuscripts (Chapters 2-4). This document was formatted in accordance with the requirements of the Graduate School at Brown University.

Chapter 1 is an introduction of the significance, rationale, and specific aims of the research conducted in the following chapters.

Chapter 2 is a version of the manuscript titled "Maternal Bacterial Infection during Pregnancy and Offspring's Risk of Psychoses: Variation by Severity of Infection and Offspring Sex," that is currently under revision at the American Journal of Psychiatry.

Chapter 3 is a version of the manuscript titled "Effects of Prenatal Bacterial Infection on Cognitive Performance in Early Childhood: Joint Inverse Probability Weighted Adjustment for Treatment and Censoring." This manuscript is currently in preparation for submission.

Chapter 4 is a version of the manuscript titled "Neurodevelopmental Impact of Prenatal Immune Activation on Memory Circuitry Structure in Early Midlife Using Structural Covariance Modeling Approach." This manuscript is also in preparation for submission. This project was supported by the Carney Institute for Brain Science at Brown University.

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I would also love to express my immense gratitude to my former advisors, Drs. Patrick Shrout and Myrna Weissman, for providing me inspiration and support to pursue a research career in psychiatric epidemiology. Lastly, I want to give my special thanks to my loving family and friends for believing in my potential and providing unconditional support.

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Chapter 1: Introduction

Across studies that use household-based survey samples, clinical diagnostic interviews, and medical records, estimates of the life-time prevalence of schizophrenia and related psychotic disorders in the U.S. range are approximately 3% (1). Despite their relatively low prevalence, psychotic disorders are associated with significant health, social, and economic burden. Approximately half of individuals with schizophrenia have co-occurring mental conditions including anxiety, depression, and addiction (2) as well as medical conditions including heart disease, liver disease, diabetes, and premature mortality (3). For this reason, financial costs associated with schizophrenia and related psychoses are disproportionately high relative to other chronic mental and physical illnesses (4).

Schizophrenia and related psychoses are characterized by delusions, hallucinations, disorganized speech, motor impairment, and cognitive impairments (5). Although symptoms typically start in late adolescence or early adulthood, psychotic illnesses are often viewed from a developmental perspective. In its simplest form, this model postulates that genes involved in neurodevelopment and environmental insults in early life lead to disruptions in brain development, which in turn predisposes to the later onset of psychosis (6,7). For example, subtle cognitive impairment and unusual behaviors sometimes appear in childhood, and persistent presence of multiple symptoms represent a later stage of the disorder (8–10). This perspective fuels the hope that early interventions will improve or prevent the course of psychotic disorders which are often severely disabling if left untreated.

Among a very limited number of potentially modifiable risk factors for psychotic disorders, maternal infection during pregnancy has been repeatedly associated with increased risk for schizophrenia (11).While epidemiologic and preclinical studies have repeatedly documented maternal viral infection during pregnancy as a putative risk factor, there is a relative

paucity of research on bacterial infection. In fact, bacterial infections are highly prevalent as a result of physiological changes and immune suppression during pregnancy, yet they are often left untreated in antenatal care settings due to their lack of apparent symptoms (12). However, such infections can pose a significant threat to pregnancy and healthy fetal development (13,14). Moreover, they may lead to severe neurodevelopmental consequences—such as mental retardation (15,16). Despite a plethora of research on the immediate impact of gestational bacterial infection on perinatal health, long-term neuropsychiatric consequences remain unclear.

The first chapter of this dissertation evaluates the potential etiologic relationship between prenatal bacterial infection and adult psychosis in adulthood—which may vary by severity of infectious exposure and offspring sex. These findings could be an important first step to motivating large-scale national register investigation of this type of research question and raise awareness of the potential neurodevelopmental consequences of prenatal bacterial infection. If replicated, they would also call for public health and clinical efforts that focus on preventing and managing bacterial infection among pregnant women and ultimately lower the burden of neurodevelopmental disorders across the lifespan.

The second chapter replicates and expands the findings from the first chapter by assessing the harmful effects of prenatal bacterial infection on cognitive outcomes in childhood that may precede the onset of psychotic illness. With this outcome, we had opportunities to address an additional potential etiologic component—such as gestational timing of exposure—and refine our etiologic model connecting prenatal bacterial infection and subsequent neurodevelopmental disorders. Furthermore, we address the concerns of potential confounding and selection bias that are inherent to non-randomized, longitudinal follow-up studies using a

combination of inverse probability of treatment and censoring weights and demonstrate the utility of this analytic technique when examining long-term outcomes of prenatal insults.

The third chapter utilizes a covariance modeling approach with structural magnetic resonance imaging (sMRI) scans to explore the putative link between prenatal bacterial infection and adult psychosis. Neurobiological research on schizophrenia and related psychoses used to focus on *single* brain regions that were thought to contain the cognitive and emotional functions disrupted by the disease. The focus has since shifted to the *interactions* between specific brain areas and, more recently, to the possibility of a global pathology affecting connections across the brain. Among several methods that have been proposed to investigate structural brain networks (17,18), techniques based on covariance modeling have been found particularly useful in several brain disorders (19–27). Included in this literature were recent publications of our group that used covariance modeling approach to examine abnormal connectivity within the working memory circuitry (28,29). We first replicate our group's previous findings of abnormal connectivity in brain regions supporting working memory functions among psychotic cases compared to healthy controls. To substantiate the possible etiologic link suggested in the first chapter, we then explored whether disturbances in the same network of brain regions would be observed upon prenatal exposure to bacterial infection.

Collectively, results from the three dissertation chapters would further scientific knowledge by clarifying the effects of prenatal bacterial infection that can contribute to the development of psychosis in adulthood. This specific knowledge would help fill gaps in the current understanding of the way in which bacterial infection during pregnancy increases offspring's risk for cognitive impairments in childhood as well as psychotic illnesses in adulthood. Findings in schizophrenia research suggests that reducing the occurrence of

gestational infection—especially among persons with a family history of psychosis or other serious mental disorder—could bring about a decline in the incidence of schizophrenia and related psychoses (11). Therefore, interventions aimed at preventing prenatal acquisition of bacterial infection and decreasing its severity may serve to lower the burden of psychosis in the United States and across the world. Such interventions may also aid in disrupting the transmission of social disparities in these neurodevelopmental disorders across generations if they target families experiencing greater socioeconomic disadvantages and thus having an increased risk for contracting infections during pregnancy.

Chapter 2: Maternal Bacterial Infection during Pregnancy and Offspring's Risk of Psychoses: Variation by Severity of Infection and Offspring Sex

2.1 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 and 15,305 unaffected offspring. 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 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: 1.9-2.3, 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.

2.2 Introduction

Epidemiologic and preclinical studies have identified maternal viral infection during pregnancy as a putative risk factor for schizophrenia (11). However, there is a relative paucity of research on bacterial infection (30–32). Bacterial infections—such as urinary tract infection and bacterial vaginosis—are highly prevalent as a result of physiological changes and immune suppression during pregnancy (12). 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 (13,14). Further, if untreated, they have been associated with severe neurodevelopmental disorders in offspring (15,16).

Despite a plethora of research 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 (30). This was replicated in another study specific to pyelonephritis (33). We previously reported that maternal immune dysregulation in general was associated with significantly higher risk of offspring psychoses (34,35), 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 (36,37). For example, murine embryos exposed to the bacterial cell wall exhibited abnormal proliferation of neuronal precursor cells, permanently altering their brain architecture (38). After birth, exposed offspring displayed behavioral, neurochemical and neurophysiologic

abnormalities consistent with observations in people with psychotic illness (38). 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 (35,39–41). 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 (42), with a substantial overlap with other psychiatric disorders (43). In fact, previous studies have demonstrated the utility of family history as a proxy of genetic liability (42,44), and one of them has specifically investigated synergistic effects of familial liability to psychosis and prenatal bacterial infection on subsequent risk for schizophrenia (33). 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 (43). 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.

2.3 Methods

2.3.1 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 (45). Details of the CPP and NEFS methodology are reported in previous publications (34,46–49). As shown in Figure 2.8.1, 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 follow-up studies of the NEFS participants, we identified those with psychoses among the original parents and offspring, now adults in their 50s (34,46–49). 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.

2.3.2 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 (49). 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 and medically edit 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.

2.3.3 Ascertainment of Exposure Status

The primary exposure variable included all 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. 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).

2.3.4 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. 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 (50) (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 (51). 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) (34). 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.

2.3.5 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 (52). 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 (43) that has also been found to be associated with infections (53). Previously, our group has reported that psychiatric history of both parents may independently predict offspring's risk for psychoses (54). 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 Collaborative Perinatal Project study—conducted at offspring's age of 7—given its strong relationship with the likelihood of being identified as a psychotic case in adulthood.

2.3.6 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, study participation at age 7, 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 (55).

2.3.7 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 2.7.3) with the confirmed instances of bacterial infection.

2.4 Results

2.4.1 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 2.7.1).

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 2.7.2). Mothers of cases were more likely to be non-white, reside in Providence, have neurologic-psychiatric conditions during pregnancy, and be less educated than mothers of non-cases.

2.4.2 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 2.7.3, 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 2.7.4, 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 multi-systemic 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 2.7.5, 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.

2.4.3 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 potential misclassification of exposure (see Table 2.9.1 through Table 2.9.3).

2.5 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 (56). Our group and others found significant associations of prenatal levels of pro-inflammatory cytokines with offspring's risk of schizophrenia and related psychoses (34,57,58) which, in a direct test, differed by sex (34). 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 (59). Although we cannot this hypothesis 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.

2.5.1 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 (34,60,61) and from others (62) 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 (63). 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 (64). 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 (65). 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 (66), consistent with our previous findings in maternal sera related to psychosis risk in males (34). 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.

2.5.2 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% (1). 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 follow-up assessment 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 (67). 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 (35), 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 (30–32). 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 (15). Several population-based studies have employed antibiotic use as a proxy of bacterial infection (68). 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 (69). 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

(70). 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.

2.6 Conclusions

There is considerable evidence that gestational viral infections during pregnancy have adverse consequences in offspring (11). 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 (38,71).

2.7 Tables

Table 2.7.1 Descriptive statistics by maternal bacterial infection during pregnancy.

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

Table 2.7.2 Descriptive statistics by adult psychosis.

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

Table 2.7.3 Associations between maternal bacterial infection during pregnancy and offspring's risk for schizophrenia and related psychoses in adulthood.

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

Abbreviations: OR, odds ratio; CI: confidence interval.

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

Table 2.7.4 Stratified analyses by offspring sex.

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

Abbreviations: OR, odds ratio; CI: confidence interval.

Table 2.7.5 Stratified analyses by parental history of mental illness (PMI).

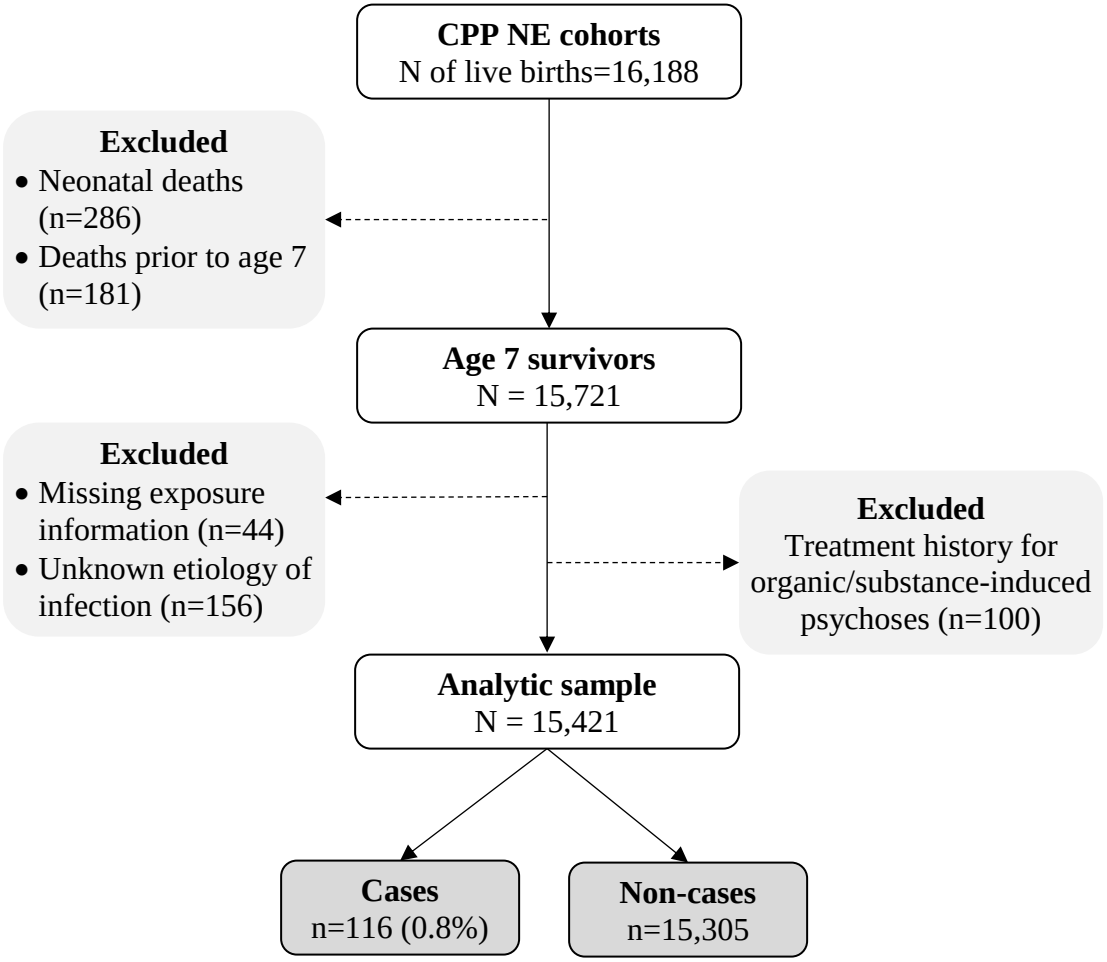
Exposure type	n_{case}*		Unadjusted OR (95% CI)			Adjusted OR (95% CI)[c]		
	PMI+	PMI-	PMI+	PMI-	*p*	PMI+	PMI-	*p*
Any bacterial infection	13	29	2.5 (1.2-5.3)	1.7 (1.1-2.7)	0.73	2.3 (1.1-5.0)[a]	1.6 (1.0-2.6)[a]	0.42
Localized bacterial infection	11	24	2.1 (1.0-4.6)	1.4 (0.9-2.3)	0.41	2.0 (0.9-4.5)[a]	1.4 (0.9-2.2)[a]	0.41
Multi-systemic bacterial infection	4	5	4.5 (1.5-13.4)[b]	2.4 (1.0-6.0)[b]	0.63	4.6 (1.5-13.8)[b,c]	2.4 (1.0-5.9)[b,c]	0.58

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

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

2.8 Figures

Figure 2.8.1 Selection of analytic sample from the New England (NE) cohorts of the Collaborative Perinatal Project (CPP).



2.9 Supplementary Materials

Table 2.9.1 Sensitivity analysis for the hypothesized associations using confirmed instances of bacterial infection.

Maternal exposure during pregnancy	n_{cases}*	Unadjusted		Adjusted	
		OR (95% CI)	*p*	OR (95% CI)	*p*
Any bacterial infection	26	2.4 (1.5-3.7)	<0.001	2.1 (1.3-3.2)[a]	0.002
Localized bacterial infection	19	1.9 (1.1-3.1)	0.016	1.7 (1.0-2.8)[a]	0.056
Multi-systemic bacterial infection	9	3.6 (1.6-7.2)	0.003	3.3 (1.4-6.5)[b]	0.006

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

Table 2.9.2 Sensitivity analyses for the stratified analyses by offspring sex.

Maternal exposure during pregnancy	n_{cases}*		Unadjusted OR (95% CI)			Adjusted OR (95% CI)		
	Male	Female	Male	Female	*p*	Male	Female	*p*
Any bacterial infection	20	6	3.2 (1.8-5.7)	1.1 (0.4-2.6)	0.037	2.9 (1.6-5.2)[a]	0.9 (0.4-2.3)[a]	0.034
Localized bacterial infection	14	8	2.3 (1.2-4.3)	1.0 (0.4-2.7)	0.18	2.0 (1.1-3.9)[a]	0.9 (0.4-2.4)[a]	0.18
Multi-systemic bacterial infection	8	1	6.1 (2.5-13.1)	-	-	5.4 (2.2-11.8)[b]	-	-

Abbreviations: OR, odds ratio; CI: confidence interval.

Table 2.9.3 Sensitivity analyses for the stratified analyses by parental mental illness (PMI).

Maternal exposure during pregnancy	n_{cases}*		Unadjusted OR (95% CI)			Adjusted OR (95% CI)		
	PMI+	PMI-	PMI+	PMI-	*p*	PMI+	PMI-	*p*
Any bacterial infection	7	18	2.5 (1.0-6.2)	2.0 (1.1-3.4)	0.70	2.2 (0.9-5.6)[a]	1.9 (1.1-3.2)[a]	0.75
Localized bacterial infection	5	13	1.8 (0.7-5.1)	1.6 (0.8-2.9)	0.79	1.7 (0.5-4.6)[b]	1.5 (0.8-2.8)[b]	0.86
Multi-systemic bacterial infection	4	5	5.0 (1.2-15.2)	2.7 (0.9-6.7)	0.41	5.3 (1.3-16.4)[b]	2.7 (0.8-6.6)[b]	0.36

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

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

Chapter 3: Effects of Prenatal Bacterial Infection on Cognitive Performance in Early Childhood: Joint Inverse Probability Weighted Adjustment for Treatment and Censoring

3.1 Abstract

Background. Long-term effects estimated from observational studies are susceptible to biases due to confounding and loss to follow-up; however, analytic techniques available to simultaneously mitigate both biases remain underutilized. We demonstrate the joint use of inverse probability treatment and censoring weights to evaluate the effects of prenatal bacterial infection on postnatal cognitive performance.

Methods. We applied inverse probability weighting for both treatment and censoring to estimate the causal effects of maternal bacterial infection during pregnancy on IQ scores measured using the Wechsler Intelligence Scale for Children at age 7. Participants (n=15,670) were members of a population-based pregnancy cohort recruited in the Boston and Providence sites of the Collaborative Perinatal Project between 1959 and 1966. We calculated Average Treatment Effects (ATE) and Average Treatment effects on the Treated (ATT) using propensity weights estimated via generalized boosted models.

Results. ATE- and ATT-weighted mean IQ scores were lowest among offspring exposed to multi-systemic bacterial infection during pregnancy and highest for those unexposed. The effects of maternal bacterial infection were greater among male offspring, particularly on performance IQ scores. Offspring who were exposed to multi-systemic bacterial infection in the third trimester had the largest decreases in full-scale, verbal, and performance IQ scores at age 7 compared to those unexposed.

Conclusions. Our study suggests causal links between prenatal bacterial infection and childhood cognitive impairments, which depend on severity and gestational timing of infectious exposure as well as offspring sex. Public health intervention targeting bacterial infection among pregnant women may have the potential to enhance the cognitive development of offspring.

3.2 Introduction

The enduring effects of prenatal insults have long been known, perhaps best illustrated by the adverse effects of prenatal exposure to toxic agents—such as infection—on postnatal physical, behavioral, and neurocognitive outcomes (72–74). Pregnant women with low levels of socioeconomic status and education, and of single marital status, are disproportionately exposed to such effects as a result of their high levels of psychosocial stress, high-risk sexual activity patterns, and limited access to health care resources (75,76). Socioeconomically disadvantaged individuals are also more likely to drop out from long-term follow-up studies (77). For this reason, exposure effects in neurodevelopmental trajectories observed in nonrandomized studies are subject to bias due to both measured and unmeasured confounding as well as selection bias (78–80). In the current study, we addressed some of these concerns using a combination of inverse probability treatment and censoring weights and demonstrated the utility of this analytic approach when examining postnatal consequences of prenatal exposures (seeSupplementary Figure 3.10.1).

Bacterial infections, including urinary tract infection and bacterial vaginosis, are highly prevalent during pregnancy due to physiological changes and immune suppression (12). Often asymptomatic, these infections may be overlooked and left untreated in antenatal care settings, potentially posing a significant threat to pregnancy and healthy fetal development (13,14). In particular, prenatal bacterial infections have been associated with severe neurodevelopmental disorders such as autism, and psychosis (30–33,81,82). While a hallmark feature shared by these neurodevelopmental disorders is the presence of childhood cognitive deficits, the relationship between cognitive function and prenatal bacterial infection remains unclear. Hence, we sought to examine whether the presence of maternal bacterial infection during pregnancy is associated with

lower cognitive performance at age 7, and also whether the strength of this association varies as a function of the severity of infectious exposure. Given the previous findings of our group (83,84) and others (85) on sexually dimorphic cognitive abilities in healthy and psychotic individuals, we hypothesized that the effects of gestational bacterial infection on cognitive deficits at age 7 are more pronounced among males than females.

There is accumulating epidemiologic as well as preclinical evidence suggesting that vulnerability to infection-mediated disturbances in fetal brain development and postnatal psychopathology varies with gestational timing of infectious exposure (86,87). First, the physiological changes experienced by the mother during pregnancy can influence the pattern of immune response (88,89). Second, it is expected that the vulnerability of the fetus to infection-mediated neurodevelopmental abnormalities critically depends on the stage of fetal development. In relation to schizophrenia, there is a debate over the suggestion that the second trimester exposure confers the maximal risk in offspring. To evaluate if this applies to earlier and less severe outcomes, such as cognitive deficits in childhood, we examined exposure to bacterial infection in which trimester of pregnancy would predict the greatest impairment in childhood cognition.

3.3 Methods

3.3.1 Participants

Participants were offspring of 15,670 singleton pregnancies enrolled during pregnancy (1959-1966) in the Massachusetts and Rhode Island cohorts of the Collaborative Perinatal Project (CPP), known as the New England Family Study (NEFS). Study psychologists evaluated these offspring's neurocognitive function at ages 4, 8, and 12 months, and 4 and 7 years using a

strict protocol and extensive quality controls (90). Details of the CPP and NEFS methodology are reported in previous publications (34,46–48,52).

3.3.2 Exposure Assessment Procedures

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 (49). Throughout the initial and repeat prenatal visits, interviewers were responsible for collection 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 for reviewing and medically editing the data collected by the interviewer, collecting further details on past and recent medical history, completing initial prenatal examination and observations, and recording 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 the participant's complete hospital records by the obstetric coordinator or a board-qualified obstetrician. Lastly, the entire study record was summarized together with the complete hospital record no later than 6 months after termination of a given pregnancy.

The primary exposure variable included all 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. 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).

Data on the timing of infection were available for multi-systemic bacterial only. We identified women with multi-systemic bacterial infections that took place in the first, second, and third trimester. Considering those who were exposed across multiple trimesters, we counted the earliest exposure to multi-systemic bacterial infection for a given pregnancy.

3.3.3 Variables in Propensity Score Model

The following measures were included in the propensity score model based on their demonstrated association with prenatal exposure to bacterial infection and/or childhood cognitive development: offspring sex, maternal age, maternal marital status, maternal race/ethnicity, socioeconomic index, and parental mental illness. Socioeconomic index in the CPP is an index based upon education-level of the head of household, occupation of head of household, and total family income (52). Parental mental illness was defined as having maternal or paternal history of treated psychiatric, substance, or neurological disorders (reported by mothers on their enrollment and at offspring's age of seven in the CPP).

3.3.4 Outcome Measures

At age 7, seven subtests from the Wechsler Intelligence Scale for Children (WISC) were administered and used to derive a full-scale IQ estimate. The vocabulary, comprehension, information, and digit span subtests were used to derive a verbal IQ estimate. The picture arrangement, block design, and digit symbol coding subtests were used to derive a performance IQ estimate. The full-scale IQ was calculated based on a combination of these two scores. The IQ data have been presented previously (67,69,91,92).

3.3.5 Statistical Analyses

We summarized the proportion of participants that were exposed to either localized, multi-systemic, or no bacterial infection during pregnancy and examined differences in baseline demographic and parental psychiatric history characteristics by exposure status. One-way ANOVA was used to test for differences in continuous variables. Chi-square tests were used to test for differences in categorical variables, one factor level at a time.

3.3.6 Propensity Score Modeling

Differences in crude IQ scores by exposure status do not account for unequal probability of being exposed to different types and gestational timing of bacterial infection during pregnancy (93). Inverse Probability of Treatment Weighting (IPTW) corrects raw IQ scores for participants' differential propensity to be exposed to certain type of bacterial infection at different timing of pregnancy, with the intent of approximating a randomized experiment (94). More than one weighting scheme is possible, each leading to different causal estimates (95).

One reweighting approach focuses on estimating Average Treatment Effects (ATEs) for all subjects, regardless of their actual exposure level (96). For example, the ATE of localized bacterial infection (hereafter, *localized*) versus no bacterial infection at all (hereafter, *none*) is the difference in mean IQ scores of the entire sample had all of its members been exposed to localized bacterial infection during pregnancy versus no bacterial infection at all. Estimating this effect requires weighting the members of the *localized* and *none* groups, so that their covariate distributions resemble that of the whole sample. After weighting, each group has similar propensity to be exposed to bacterial infection during pregnancy. The weighted differences in mean IQ scores between the two exposure groups then serve as estimates of the ATE of localized infection. We estimated these weights non-parametrically using Generalized Boosted Model

(GBM) as implemented in the GBM package (97), thus gaining robustness to possible misspecification of the propensity score model.

A second reweighting approach is based on estimating Average Treatment Effects on the Treated (ATTs) separately for each exposure group (96). When multivalued treatments are involved, it is recommended that separate GBMs be fit to each pair of groups involved in the comparison of interest, ignoring any remaining groups (95). Unit weights are assigned to target group members, while those in the reference group have their mean IQ scores weighted by the odds that they would have exhibited the target behavior. Individuals in the reference group with covariate values common in their own group alone are down-weighted, whereas those with values common in the target group are up-weighted.

Weighted estimates calculated under an ATT approach allow one to make group-specific inferences and to gauge the effect of moving study participants from one exposure group to another. However, the findings may not apply to all participants involved in a pairwise comparison, as near-zero propensity scores would imply that certain subjects are unlikely to ever experience the target exposure. Near-zero propensity scores correspond to near-infinite weights and have the potential to drastically reduce the effective sample size of the reference group involved in each comparison, defined as the size of a simple random sample with same standard error as the ATT-weighted mean. For example, the ATT of localized bacterial infection versus no bacterial infection at all in the *localized* group is the difference between (i) the actual mean IQ score of the *localized* group, and (ii) the mean IQ score of this same group, had none of its member been prenatally exposed to bacterial infection at all. Estimating this effect requires weighting the *none* group, so that its covariate distribution resembles that of the *localized* group; the mean IQ score in the weighted *none* group then serves as an estimate for the mean IQ of the

localized group under no exposure. For both ATE and ATT analyses, individual GBM fits were weighted combinations of up to 10,000 trees of depth two, capturing both main effects and 2-way interactions in model covariates (98). A shrinkage parameter of 0.01 was used for smoothing, and absolute standardized bias was used for selecting the number of trees providing the best covariate balance.

Given the longitudinal nature of the NEFS, the dropout rate at age 7 was 23.2%—which created a large number of missing observations in the outcome variables. Inverse Probability of Censoring Weighting (IPCW) adjusts raw IQ scores for selection bias and dropout in the context of longitudinal follow-up study. It inversely weights regression analyses by the probability of not dropping out and effectively inflates the impact of underrepresented participants (99–101). This way, we can observe associations that would have been observed if all participants had stayed in the study. We estimated the final inverse probability weights by multiplying IPCW with IPTW (102).

3.3.7 Outcome Modeling

At age 7, seven subtests from the Wechsler Intelligence Scale for Children (WISC) were administered and used to derive a full-scale IQ estimate. The vocabulary, comprehension, information, and digit span subtests were used to derive a verbal IQ estimate. The picture arrangement, block design, and digit symbol coding subtests were used to derive a performance IQ estimate. The full-scale IQ was calculated based on a combination of these two scores. The IQ data have been presented previously (67,69,91,92).

3.4 Results

3.4.1 Description of the Study Sample

Among 15,670 study participants, 12,113 (77.3%) were exposed to no bacterial infection, 3,155 (20.1%) were exposed to localized bacterial infection, and 402 (2.6%) were exposed to multi-systemic bacterial infection (see Table 1). Prenatal exposure to these three levels of bacterial infection defines groups of interest in this study: *None*, *Localized*, and *Multi-systemic*. Of note, 91 participants who were exposed to both localized and multi-systemic bacterial infection are classified under the *Multi-systemic* group. Among 402 participants who were exposed to multi-systemic bacterial infection, 122 (30.3%) were exposed in the first trimester, 137 (34.1%) were exposed in the second trimester, and 143 (35.6%) were exposed in the third trimester (see Table 3.9.2).

Table 3.7.1 shows between-group differences in demographic and family history variables used as potential confounders in our propensity scores model. Offspring whose mother was non-married, non-white, younger, and had low socioeconomic status were more likely to have been exposed to multi-systemic bacterial infection during pregnancy. In contrast, offspring whose mother was married, white, older, and had high socioeconomic status, were most likely to have been unexposed to bacterial infection during pregnancy. Parental history of mental illness was most prevalent among offspring exposed to multi-systemic bacterial infection (17.3%) and more prevalent among those exposed to localized bacterial infection (13.5%) compared to those unexposed (10.8%). The unweighted means of full-scale, verbal, and performance IQ scores differed significantly across the exposure categories defined by severity of infectious exposure, being highest among those unexposed and lowest among those exposed to multi-systemic bacterial infections. Similarly, the unweighted means in the IQ measures were highest among

those unexposed to multi-systemic bacterial infection and lowest among those exposed in the third trimester. Of note, patterns of missingness in the IQ measures did not differ by severity or gestational timing of infectious exposure.

3.4.2 Weighting and Balance Diagnostics

Improvements in covariate balance were assessed based on change in absolute standardized bias measures (103,104). For continuous covariates, these were between-group mean differences before and after weighting, divided by the unweighted standard deviation of the full sample or the target exposure group. For categorical variables, separate standardized bias measures were calculated for each covariate level, based on between-group differences in proportions. In addition, differences in spread were assessed by examining between-group ratio of variances before and after weighting. Formal significance testing was avoided in assessing covariate balance (105). Rather, absolute bias measures smaller than 0.25 standard units and variance ratios in the interval [4/5,5/4] were deemed indicative of successful balancing (106,107). Once a propensity model was deemed adequate, weights (i.e., the product of IPTW and IPCW) were fed from the GBM package into the SURVEY package (108) and used to calculate point and interval estimates of differences in weighted mean IQ scores by exposure status.

Estimated probabilities of observing the actual exposure to bacterial infection with varying severity of exposure during pregnancy were in the ranges of 0.45-0.93 for no exposure, 0.09-0.56 for localized infection, and 0.02-0.15 for the multi-systemic infection. As a result, reductions in the effective sample size of the reference group in ATT analyses were in the 20-30% range for the two pairwise comparisons involving multi-systemic bacterial infection, but

remained below 9% for comparisons involving localized bacterial infection and no exposure (see Table 3.9.2).

Estimated probabilities of observing multi-systemic bacterial infection occurring at different stage of pregnancy were in the ranges of 0.79-0.99 for no exposure, 0.01-0.08 for first trimester exposure, 0.01-0.15 for second trimester exposure, and 0.01-0.06 for third trimester exposure. As a result, reductions in the effective sample size of the reference group in ATT analyses were in the 45-60% range for the three pairwise comparisons involving no exposure, but remained below 36% for other comparisons. Balance diagnostics for variables in Tables 1 and 2 showed that all absolute bias measures fell below 0.25 standard units after weighting (see Figure 3.10.2 (a)-(c) and Figure 3.10.3 (a)-(d)).

3.4.3 Unweighted Analyses

Compared to unexposed offspring, those exposed to localized or multi-systemic bacterial infection had lower mean full-scale IQ scores at age 7. Offspring who were exposed to multi-systemic bacterial infection had significantly lower IQ scores than those exposed to localized bacterial infection, thus establishing an inverse relationship of mean IQ scores at age 7 with the severity of infectious exposure during pregnancy (see Figure 3.4.1). Similar patterns of association were observed for all IQ measures examined. In general, the effect sizes were greater among males than females (see Figure 3.8.2 and Figure 3.8.3). Offspring who were exposed in the third trimester had significantly lower mean IQ scores. They also had significantly lower mean IQ scores relative to those exposed in the first or second trimester for all types of IQ measures examined (see Figure 3.8.4).

3.4.4 ATE-Weighted Analyses

ATE-weighted mean IQ scores differ from observed scores due to a reweighting scheme that brings group-specific covariate distributions closer to those of the overall sample. ATE findings are bidirectional and apply to the entire sample. For example, the expected 2.47-point decrease in mean IQ had the entire sample had multi-systemic bacterial infection instead of no bacterial infection is equal in magnitude and opposite in sign to the 2.47-point increase in mean IQ if the entire sample had localized bacterial infection instead of systemic bacterial infection. Thus, only 3 out of 6 possible comparisons are presented in Supplementary Table 3.9.4 through Supplementary Table 3.9.6).

Compared to the unweighted analyses, we observed a general reduction in the magnitude of effects in the ATE-weighted analyses; however, the findings were consistent in terms of the interpretation. For example, multi-systemic bacterial infection during pregnancy had a greater effect on mean full-scale, verbal, and performance IQ scores than did localized bacterial infection, indicating that the effects were dependent upon severity of infectious exposure (see Figure 3.8.1 and Supplementary Table 3.9.4).

As in the unweighted analysis, we observed generally stronger effects of prenatal bacterial infection on mean IQ scores in the male stratum than in the unstratified sample; the effects were particularly strong on performance IQ among male offspring (see Figure 3.8.2 and Supplementary Table 3.9.5). In contrast, we observed no effect of prenatal bacterial infection on any IQ measures among female offspring (see Figure 3.8.3 and Supplementary Table 3.9.6).

For all types of IQ measures examined, offspring who were exposed in the third trimester had significantly lower mean IQ scores compared to exposed in the first or second trimester, as well as those unexposed (see Figure 3.8.4 and Supplementary Table 3.9.7).

3.4.5 ATT-Weighted Analyses

ATT-weighted mean IQ scores are shown in Table 2 and differ from observed scores due to a reweighing scheme that brings the covariate distributions of severity and gestational timing of each infectious exposure closer to that of a target exposure group, rather than to the sample as a whole. They supplement ATE findings and permit unidirectional predictions for all 6 possible pairwise comparisons.

Had unexposed offspring been prenatally exposed to multi-systemic or localized bacterial infection, their mean full-scale, verbal and performance IQ scores would have decreased (see Figure 3.8.1 and Supplementary Table 3.9.4). Conversely, offspring exposed to multi-systemic infection would have had increased mean full-scale, verbal and performance IQ scores had they been unexposed or exposed to less severe, localized bacterial infection. These ATT-weighted effects were much reduced for localized bacterial infection, thus indicating that they are dependent on severity of infectious exposure. In general, these ATT-weighted effects are nearly twice as large in the male stratum, but failed to attain statistical significance in the female stratum (see Figure 3.8.2 - Figure 3.8.3 and Supplementary Table 3.9.5 - Supplementary Table 3.9.6).

Had unexposed offspring been exposed to multi-systemic bacterial infection in the third trimester, there would have been a substantial decrease in their mean full-scale, verbal, and performance IQ scores (see Figure 3.8.4 and Supplementary Table 3.9.7). Conversely, offspring exposed in the third trimester would have had much higher mean full-scale, verbal, and performance IQ scores had they been unexposed or exposed in earlier trimesters. Similarly, offspring exposed in second trimester would have had significantly lower mean full-scale and verbal IQ scores had they been exposed in the third trimester; however, none of the IQ scores

would have changed had they been exposed in the first trimester. These ATT-weighted results indicate that the effects of multi-systemic bacterial infection are dependent upon gestational timing of exposure, with late gestational exposure being more harmful than early or mid-gestational exposure.

3.5 Discussion

To our knowledge, this study is the first to attempt to estimate the causal impact of bacterial infection during pregnancy for childhood cognitive deficits using methods to jointly account for measured confounding and selection bias due to loss to follow-up using propensity weights.

Unweighted data analyses for severity of infection suggested that both localized and multi-systemic bacterial infection reduced mean IQ scores at age 7 over no exposure to bacterial infection during pregnancy, and ATE weighted analyses applied to the entire analytic sample strengthened this conclusion. ATT weighted analyses applied separately by group reaffirmed findings of harmful effects of multi-systemic bacterial infection on fetal cognitive development at age 7. In contrast, ATT estimates of the effects of exposure to localized bacterial infection were largely attenuated, with only a small reduction in mean IQ scores expected as a result of exposure among previously unexposed offspring. There was also a small increase in mean IQ scores of previously exposed offspring under the counterfactual condition of no exposure to any bacterial infection during pregnancy. Similar overall patterns of effects, but of even greater magnitude, were observed among male offspring.

Unweighted analyses for gestational timing revealed that only third trimester exposure to multi-systemic bacterial infection significantly reduced mean IQ scores at age 7 up to 7 points over no exposure to this type of infection. ATE-weighted analyses strengthened this conclusion,

yielding overall reduction in full-scale, verbal, and performance IQ scores by 4.45 points, 4.13 points, and 3.25 points. ATT weighted analyses potentially identified third trimester as the gestational timing during which multi-systemic bacterial infection might be most harmful for the cognitive development of offspring (i.e., sensitive period), with a dramatic reduction in mean IQ scores of unexposed offspring under third trimester exposure, and a large increase in mean IQ scores of offspring exposed in the third trimester under no prenatal exposure to this type of infection.

The current study provides epidemiologic evidence that identifies third trimester (i.e., late pregnancy) as the sensitive period for cognitive abnormalities in early childhood. In fact, the timing of prenatal immune challenge seems to determine phenotypic specificity of inflammation-mediated brain and behavioral pathology. For example, early to mid-gestational immune challenges are reported to affect the development of central dopaminergic system and lead to a more global deterioration of brain function (109,110). In contrast, late gestational challenges are reported to interfere especially with the refinement of connections through pruning (111,112), the long-term consequences of which may specifically lead to selective and mild cognitive impairments (87). Our findings are in full agreement with these preclinical findings and readily suggest that late gestational exposure to bacterial infection might precipitate cognitive disturbances emerging in later life, as early as the age of seven.

3.5.1 Sex Differences in Cognitive Deficits during Early Childhood

Our findings suggest that maternal bacterial infection during pregnancy may affect postnatal cognitive functioning primarily among male offspring. Some have suggested the role of the placenta in mediating this effect, in that the placenta of females may possess greater ability to adapt to fluctuating environmental conditions compared to that of males (63). However, the

mechanism underlying a male-specific vulnerability remains 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 (64).

In fact, our group has recently reported male-specific effects of maternal bacterial infection during pregnancy on psychosis risk (81). One possible implication is that the cognitive deficits in early childhood may mediate the relationship between prenatal bacterial infection and the pathogenesis of such neurodevelopmental disorders in a sex-dependent manner. Studies of subjects at high risk for schizophrenia have identified significantly more premorbid abnormalities among boys than among girls in cognition and attention (113,114). These studies and our group's earlier work (115) suggest that these sex differences in early developmental deficits may persist into adulthood, potentially explaining why psychotic men may have more severe neurocognitive consequences than psychotic women.

3.5.2 Strengths and Limitations

Compared to our estimates, prior findings in the literature imply more harmful effects of prenatal infection that also appear to be statistically significant. It is hard to compare our results directly with those of prior studies because we have based our analysis on propensity-weighted models. Estimates of the effect of exposure to bacterial infection from unweighted analyses are potentially biased due to confounding and loss to follow up. In contrast, we expect that parameters from our propensity models to be unbiased estimates of the causal relations between the prenatal infectious exposures and cognitive development in offspring, under the assumption of no unmeasured confounders and correct specification of the propensity model (99). As our GBM estimation approach is non-parametric, model mis-specification issues are unlikely to be very impactful. Although we cannot be certain about the untestable assumption of no

unmeasured confounding, we have included in the propensity model all those factors that we regarded as potentially confounding the exposure-to-outcome relationship. Therefore, we expect our estimates to be less biased than those derived from studies that failed to account for differential probability of being exposed to bacterial infection during pregnancy and of dropping out during follow up.

Our study also had a limitation that 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 (30–32). 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. Nevertheless, we demonstrated the validity of our exposure measurement in the previous investigation through cross-validation with alternative sources of information including medical diagnosis by physician and treatment history with antibacterial medications (81).

3.6 Conclusions

In summary, we applied propensity modeling to explore causal relationships of bacterial infection during pregnancy and measures of cognitive performances at age 7. We examined whether the hypothesized effects of prenatal bacterial infection on mean IQ scores would vary as a function of severity and gestational timing of exposure. We discovered that the more severe type of bacterial infection (i.e., multi-systemic) resulted in a greater reduction in mean IQ scores at age 7, especially among male offspring. We also found that third trimester exposure to multi-systemic bacterial infection predicted greater childhood cognitive deficits than exposures in earlier trimesters. Findings in this study underscore the potential role of maternal bacterial

infection during pregnancy in the developmental trajectory of cognitive functions in offspring. They call for additional investigation and, if replicated, potentially 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.

3.7 Tables

Table 3.7.1 Demographic and family history characteristics by severity of bacterial infection during pregnancy.

	Maternal bacterial infection during pregnancy			
	None	***Localized***	***Multi-systemic***	***p***
Total N (%)	12113 (77.3)	3155 (20.1)[a]	402 (2.6)	
Categorical variables, n (%)				
Offspring sex				0.67
Male	6189 (51.1)	1585 (50.2)	202 (50.2)	
Female	5915 (48.8)	1568 (49.7)	199 (49.5)	
Maternal marital status				<0.001
Married	10925 (90.2)	2726 (86.4)	339 (84.3)	
Non-married	1186 (9.8)	429 (13.6)	63 (15.7)	
Maternal race/ethnicity				<0.001
White	10526 (86.9)	2647 (83.9)	333 (82.8)	
Black	1387 (11.5)	469 (14.9)	63 (15.7)	
Oriental	112 (0.9)	20 (0.6)	1 (0.2)	
Puerto Rican	24 (0.2)	6 (0.2)	2 (0.5)	
Other	64 (0.5)	13 (0.4)	3 (0.7)	
Socioeconomic index (quartiles)				<0.001
1st quartile (Lowest)	3069 (26.5)	906 (29.7)	142 (36.5)	
2nd quartile	3123 (26.9)	867 (28.4)	104 (26.7)	
3rd quartile	2657 (22.9)	674 (22.1)	65 (16.7)	
4th quartile (Highest)	2746 (23.7)	603 (19.8)	78 (20.1)	
Parental history of mental illness				
Present	1295 (10.9)	419 (13.6)	68 (17.2)	<0.001
Not present	10535 (89.1)	2673 (86.4)	328 (82.8)	
Missing full-scale IQ at age 7	2874 (23.7)	723 (22.9)	88 (21.9)	0.47
Missing verbal IQ at age 7	2938 (24.3)	743 (23.5)	92 (22.9)	0.61
Missing performance IQ at age 7	2936 (24.2)	743 (23.5)	92 (22.9)	0.62
Continuous variables, mean (sd)				
Maternal age	25.2 (5.9)	24.9 (5.9)	24.7 (5.7)	0.031
Full-scale IQ	102.1 (14.2)	100.8 (14.2)	98.8 (15.0)	<0.001
Verbal IQ	100.3 (14.0)	99.0 (14.1)	97.4 (14.5)	<0.001
Performance IQ	104.2 (14.3)	103.2 (14.1)	101.5 (15.1)	<0.001

Abbreviations: IQ, intelligence quotient.

3.8 Figures

Figure 3.8.1 Full-scale intelligence quotient (IQ) estimates and corresponding 95% confidence intervals by severity of bacterial exposure.

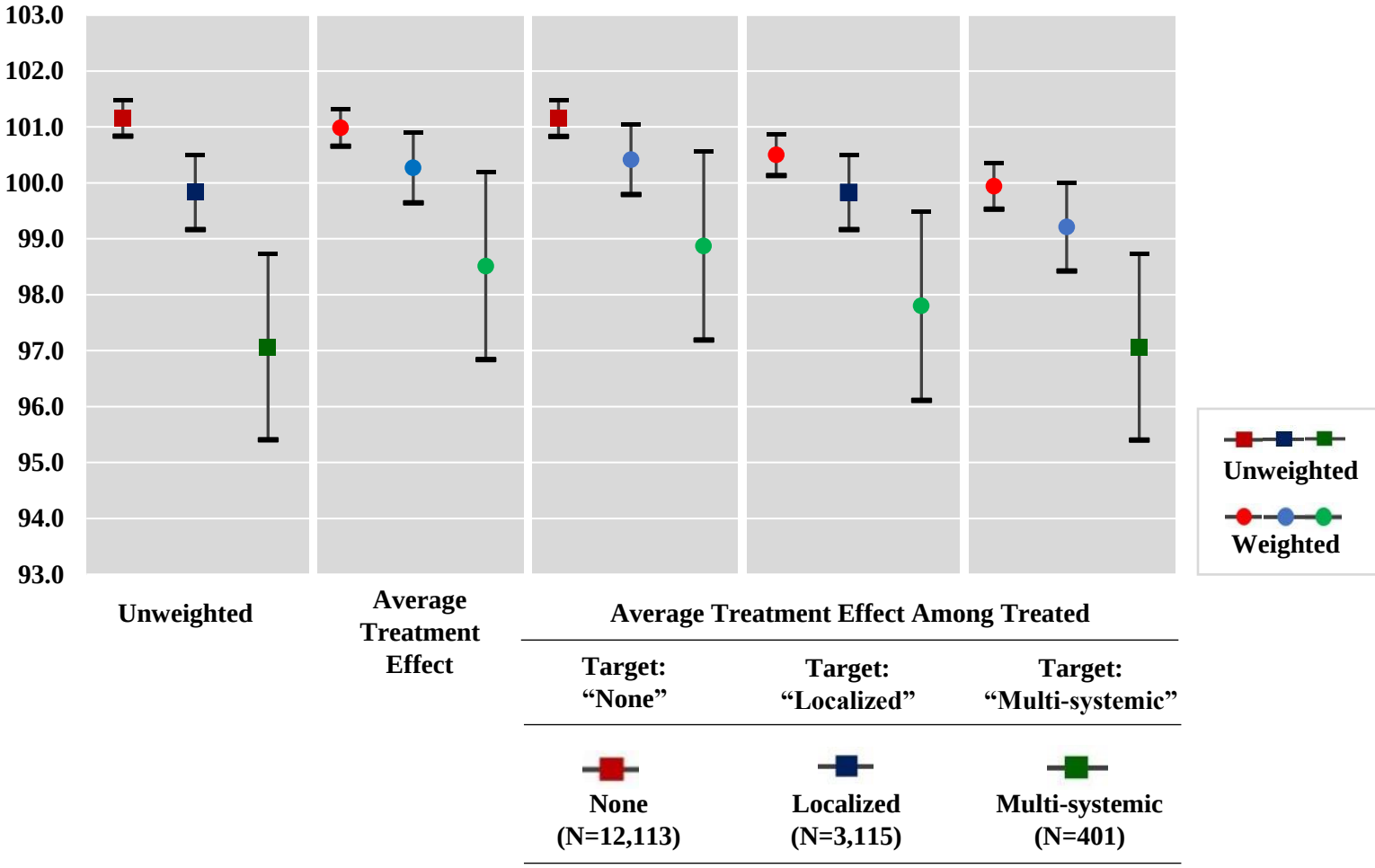


Figure 3.8.2 Male-specific full-scale intelligence quotient (IQ) estimates and corresponding 95% confidence intervals by severity of bacterial exposure.

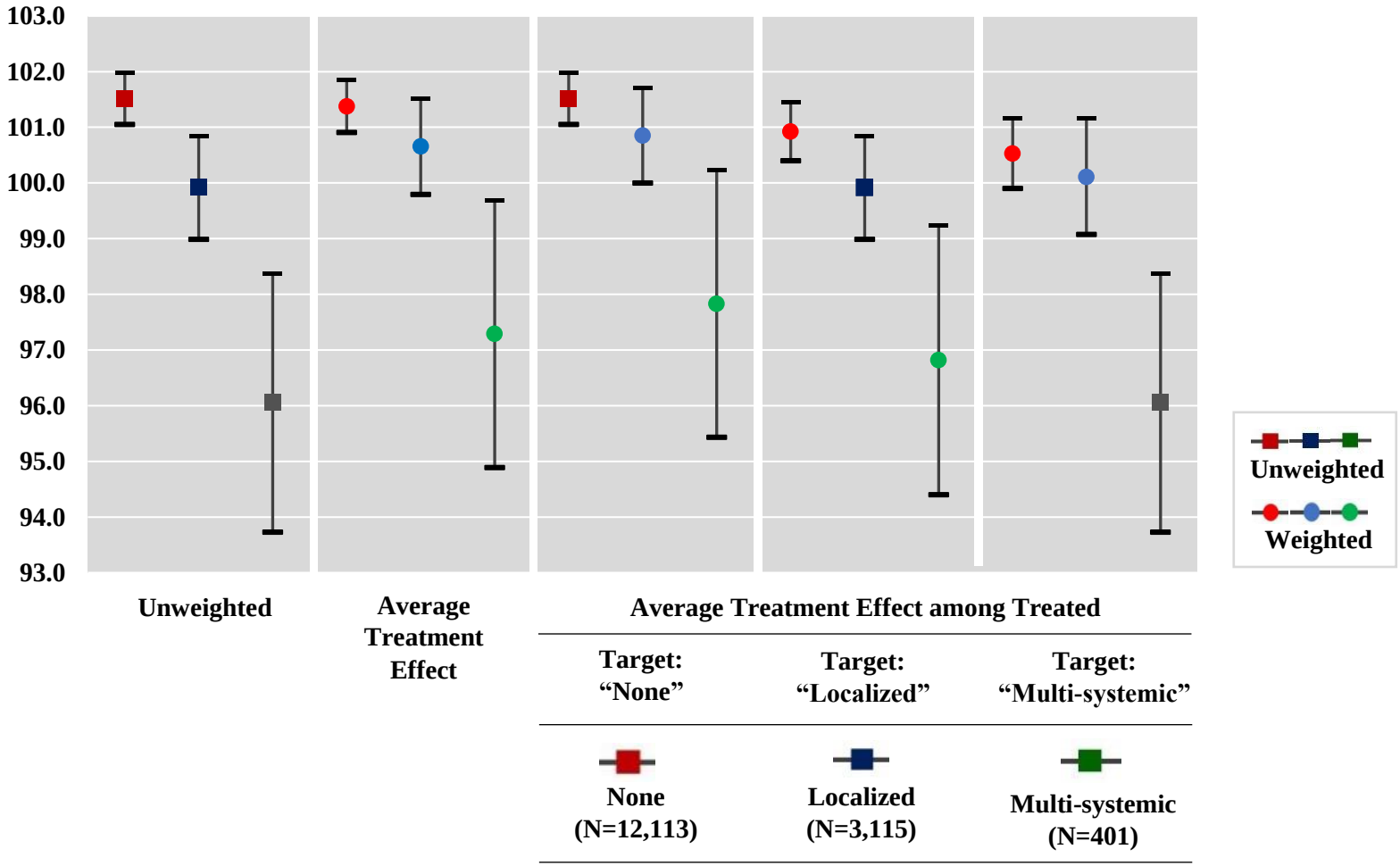


Figure 3.8.3 Female-specific full-scale intelligence quotient (IQ) estimates and corresponding 95% confidence intervals by severity of bacterial infection.

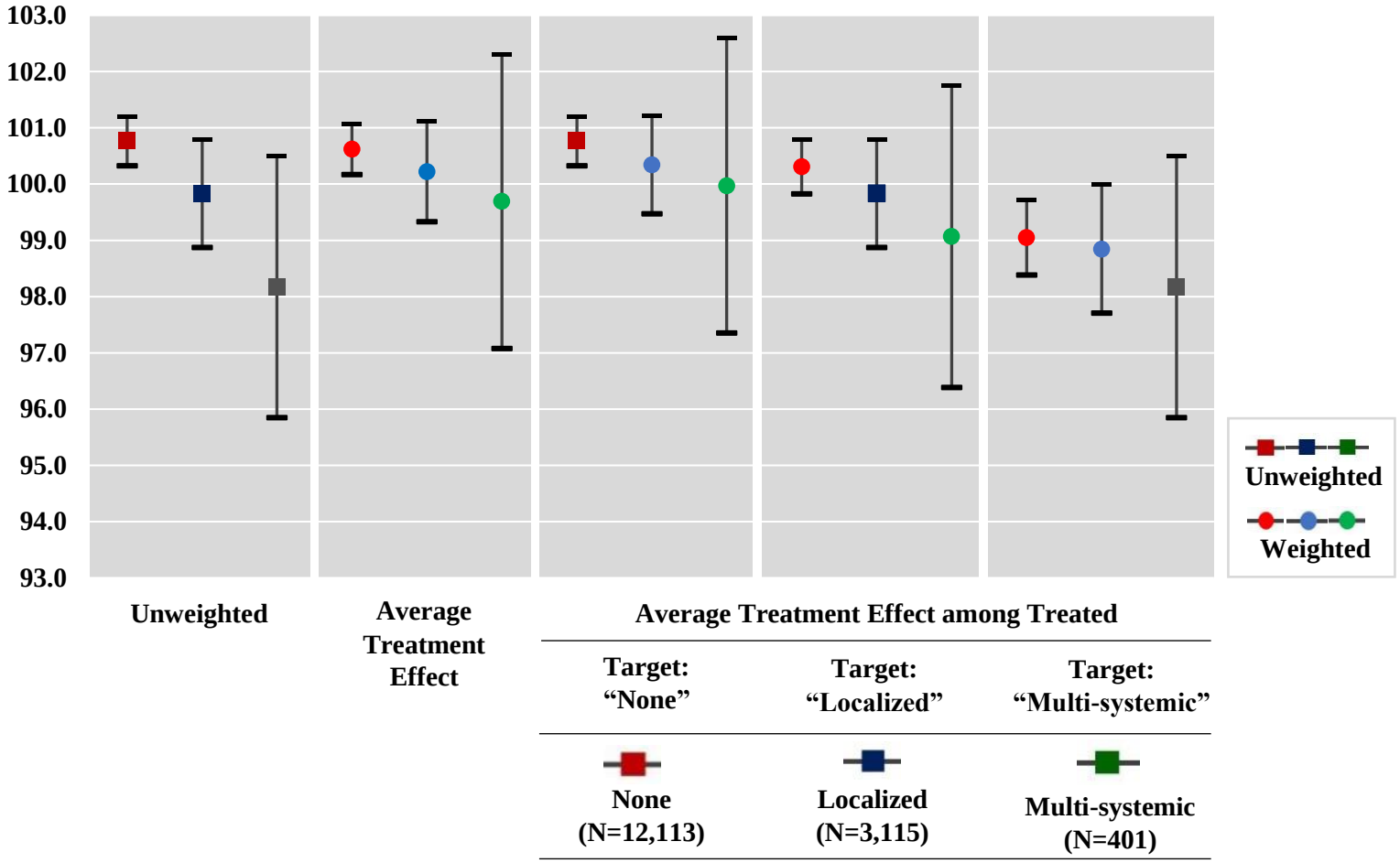
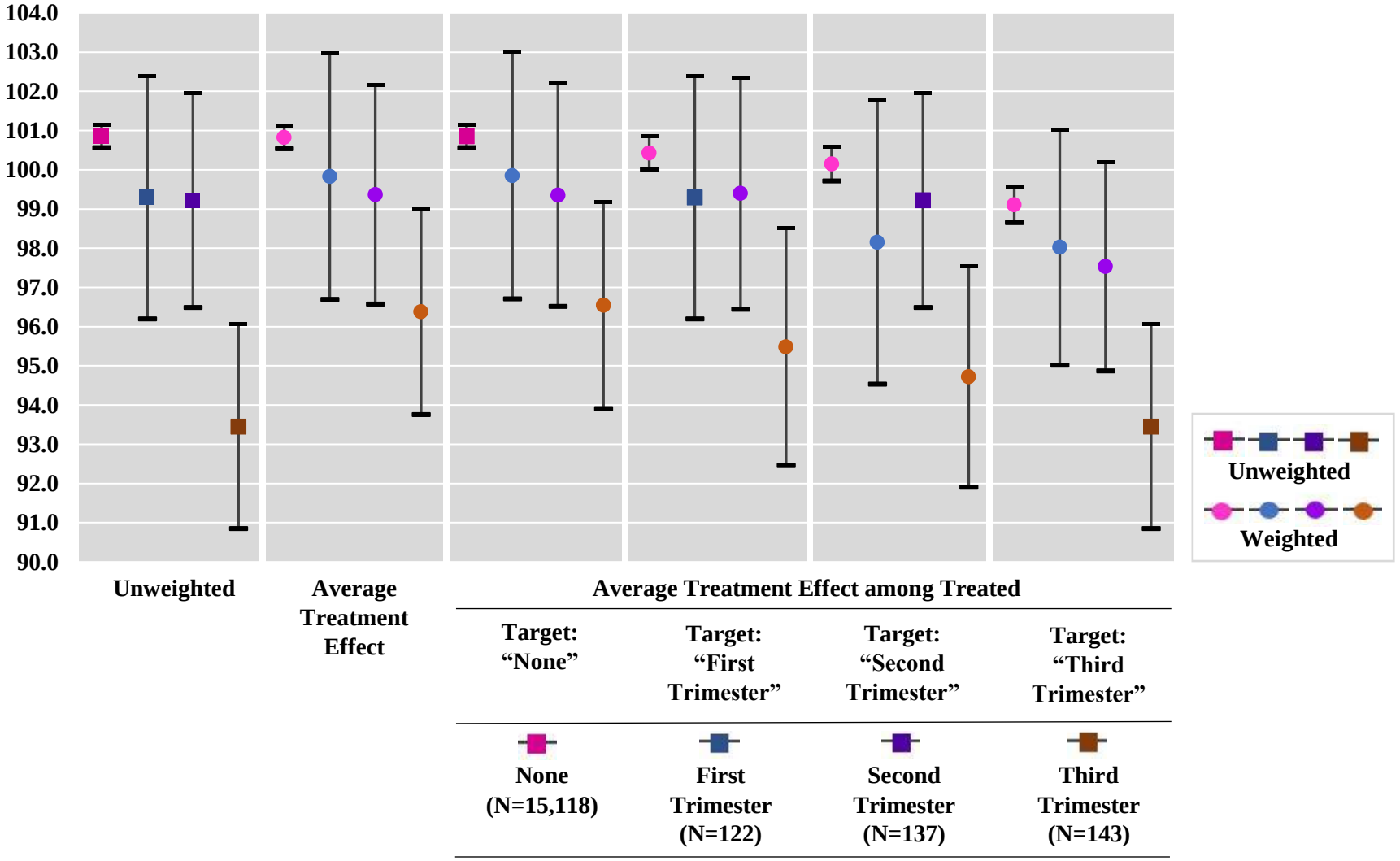


Figure 3.8.4 Full-scale intelligence quotient (IQ) estimates and corresponding 95% confidence intervals by gestational timing of exposure to multi-systemic bacterial infection before and after propensity score weighting.



3.9 Supplementary Tables

Table 3.9.1 Demographic and family history characteristics by gestational timing of exposure to multi-systemic bacterial infection during pregnancy.

	Trimester of exposure to multi-systemic bacterial infection				
	None	***First***	***Second***	***Third***	***p***
Total N (%)	15118 (97.4)	122 (0.8)	137 (0.9)	143 (0.9)	<0.001
Categorical variables, n (%)					
Offspring sex					<0.001
Male	7702 (50.9)	61 (50.0)	73 (53.3)	68 (47.6)	
Female	7414 (49.0)	61 (50.0)	63 (46.0)	75 (52.4)	
Maternal marital status					0.093
Married	1604 (10.6)	19 (15.6)	20 (14.6)	24 (16.8)	
Non-married	13512 (89.4)	103 (84.4)	117 (85.4)	119 (83.2)	
Maternal race/ethnicity					0.27
White	13043 (86.3)	102 (83.6)	113 (82.5)	118 (82.5)	
Non-White	2075 (13.7)	20 (16.4)	24 (17.5)	25 (17.5)	
Socioeconomic index (quartiles)					<0.001
1st quartile (Lowest)	3957 (26.2)	36 (29.5)	40 (29.2)	66 (46.2)	
2nd quartile	3971 (26.3)	31 (25.4)	40 (29.2)	33 (23.1)	
3rd quartile	3312 (21.9)	25 (20.5)	21 (15.3)	19 (13.3)	
4th quartile (Highest)	3300 (21.8)	28 (23.0)	29 (21.2)	21 (14.7)	
Parental history of mental illness					0.014
Present	13111 (86.7)	101 (82.8)	107 (78.1)	120 (83.9)	
Not present	1703 (11.3)	20 (16.4)	26 (19.0)	22 (15.4)	
Missing full-scale IQ	3492 (23.1)	24 (19.7)	35 (25.5)	29 (20.3)	0.59
Missing verbal IQ	3575 (23.6)	24 (19.7)	36 (26.3)	32 (22.4)	0.63
Missing performance IQ	3573 (23.6)	24 (19.7)	36 (26.3)	32 (22.4)	0.63
Continuous variables, mean (sd)					
Maternal age	25.1 (5.9)	24.3 (5.4)	24.9 (5.6)	24.9 (6.0)	0.44
Full-scale IQ	101.8 (14.2)	101.4 (15.2)	100.3 (14.3)	95.3 (15.0)	<0.001
Verbal IQ	100.0 (14.0)	99.8 (14.4)	98.5 (15.0)	94.3 (13.7)	<0.001
Performance IQ	104.0 (14.3)	102.9 (15.8)	102.6 (15.1)	99.3 (14.2)	0.004

Abbreviations: IQ, intelligence quotient.

Table 3.9.2 Nominal and effective sample sizes by severity of bacterial infection under ATT* weighting.

	Target Group			
Reference Group	***Nominal***	***None***	***Localized***	***Multi-systemic***
None	12113	-	11314	8518
Localized	3155	3010	-	2506
Multi-systemic	402	367	384	-

Table 3.9.3 Nominal and effective sample sizes by gestational timing of multi-systemic bacterial infection under ATT* weighting.

	Target Group				
Reference Group	***Nominal***	***None***	***First***	***Second***	***Third***
None	15118	-	8138	6308	6823
First	122	117	-	99	97
Second	137	112	100	-	88
Third	143	118	112	108	-

* ATT, average treatment effect among treated.

Table 3.9.4 Mean intelligence quotient (IQ) estimates at age 7 by severity of bacterial exposure during pregnancy in the full analytic sample.

			Full-Scale IQ	Verbal IQ	Performance IQ
			ΔMean (95% CLs)†	*ΔMean (95% CLs)*†	*ΔMean (95% CLs)*†
Unweighted analyses					
Localized	vs.	None	-1.32 (-2.04, -0.61)	-1.37 (-2.07, -0.66)	-1.08 (-1.80, -0.36)
Multi-systemic	vs.	None	-4.09 (-5.87, -2.31)	-3.54 (-5.3, -1.78)	-3.67 (-5.47, -1.88)
Multi-systemic	vs.	Localized	-2.77 (-4.71, -0.82)	-2.18 (-4.11, -0.25)	-2.59 (-4.56, -0.63)
ATE weighted analyses					
Localized	vs.	None	-0.71 (-1.42, 0.00)	-0.71 (-1.41, -0.01)	-0.62 (-1.33, 0.10)
Multi-systemic	vs.	None	-2.47 (-4.18, -0.76)	-2.27 (-3.98, -0.56)	-2.04 (-3.83, -0.25)
Multi-systemic	vs.	Localized	-1.76 (-3.55, 0.029)	-1.56 (-3.36, 0.23)	-1.42 (-3.29, 0.45)
ATT weighted to match "None"					
Localized	vs.	None	-0.73 (-1.44, -0.03)	-0.72 (-1.41, -0.03)	-0.63 (-1.34, 0.08)
Multi-systemic	vs.	None	-2.28 (-3.99, -0.56)	-2.12 (-3.83, -0.41)	-1.80 (-3.60, -0.01)
ATT weighted to match "Localized"					
None	vs.	Localized	0.67 (-0.09, 1.43)	0.76 (0.02, 1.50)	0.59 (-0.16, 1.34)
Multi-systemic	vs.	Localized	-2.03 (-3.85, -0.21)	-1.69 (-3.52, 0.15)	-1.76 (-3.66, 0.13)
ATT weighted to match "Multi-systemic"					
None	vs.	Multi-systemic	2.88 (1.16, 4.59)	2.21 (0.45, 3.97)	2.75 (0.87, 4.62)
Localized	vs.	Multi-systemic	2.15 (0.31, 3.99)	1.51 (-0.36, 3.39)	2.09 (0.09, 4.09)

Abbreviations: CL, confidence limit; ATE, average treatment effect; ATT, average treatment effect among treated.

† Differences are calculated as 1st group - 2nd group, where pairs are expressed as "1st group vs. 2nd group."

Table 3.9.5 Mean intelligence quotient (IQ) estimates at age 7 by severity of bacterial exposure during pregnancy among male offspring.

			Full-Scale IQ	Verbal IQ	Performance IQ
			ΔMean (95% CLs)†	*ΔMean (95% CLs)*†	*ΔMean (95% CLs)*†
Unweighted analyses					
Localized	vs.	None	-1.60 (-2.63, -0.56)	-1.54 (-2.54, -0.54)	-1.38 (-2.42, -0.34)
Multi-systemic	vs.	None	-5.46 (-8.08, -2.85)	-4.63 (-7.14, -2.12)	-5.75 (-8.38, -3.13)
Multi-systemic	vs.	Localized	-3.86 (-6.61, -1.12)	-3.08 (-5.79, -0.38)	-4.37 (-7.16, -1.58)
ATE weighted analyses					
Localized	vs.	None	-0.72 (-1.71, 0.26)	-0.70 (-1.66, 0.27)	-0.68 (-1.69, 0.34)
Multi-systemic	vs.	None	-4.09 (-6.53, -1.64)	-3.58 (-6.12, -1.04)	-4.26 (-6.85, -1.67)
Multi-systemic	vs.	Localized	-3.37 (-5.92, -0.81)	-2.89 (-5.53, -0.25)	-3.58 (-6.28, -0.88)
ATT weighted to match "None"					
Localized	vs.	None	-0.66 (-1.63, 0.32)	-0.66 (-1.61, 0.30)	-0.61 (-1.61, 0.40)
Multi-systemic	vs.	None	-3.68 (-6.13, -1.24)	-3.31 (-5.84, -0.78)	-3.78 (-6.34, -1.22)
ATT weighted to match "Localized"					
None	vs.	Localized	1.01 (-0.06, 2.07)	0.91 (-0.14, 1.95)	1.00 (-0.07, 2.07)
Multi-systemic	vs.	Localized	-3.10 (-5.69, -0.50)	-2.53 (-5.19, 0.13)	-3.58 (-6.37, -0.80)
ATT weighted to match "Multi-systemic"					
None	vs.	Multi-systemic	4.48 (2.07, 6.89)	3.59 (1.03, 6.15)	4.91 (2.17, 7.64)
Localized	vs.	Multi-systemic	4.06 (1.51, 6.61)	3.17 (0.49, 5.86)	4.51 (1.63, 7.39)

Abbreviations: CL, confidence limit; ATE, average treatment effect; ATT, average treatment effect among treated.

† Differences are calculated as 1st group - 2nd group, where pairs are expressed as "1st group vs. 2nd group."

Table 3.9.6 Mean intelligence quotient (IQ) estimates at age 7 by severity of bacterial exposure during pregnancy among female offspring.

			Full-Scale IQ	Verbal IQ	Performance IQ
			ΔMean (95% CLs)†	*ΔMean (95% CLs)*†	*ΔMean (95% CLs)*†
Unweighted analyses					
Localized	vs.	None	-0.93 (-1.92, 0.06)	-1.11 (-2.10, -0.12)	-0.65 (-1.63, 0.33)
Multi-systemic	vs.	None	-2.60 (-5.00, -0.19)	-2.37 (-4.81, 0.07)	-1.50 (-3.90, 0.92)
Multi-systemic	vs.	Localized	-1.67 (-4.50, 1.07)	-1.26 (-4.04, 1.52)	-0.84 (-3.60, 1.92)
ATE weighted analyses					
Localized	vs.	None	-0.40 (-1.39, 0.60)	-0.52 (-1.52, 0.48)	-0.26 (-1.24, 0.72)
Multi-systemic	vs.	None	-0.93 (-3.58, 1.72)	-0.98 (-3.53, 1.57)	0.11 (-2.55, 2.78)
Multi-systemic	vs.	Localized	-0.53 (-3.29, 2.23)	-0.46 (-3.12, 2.21)	-0.37 (-2.40, 3.14)
ATT weighted to match "None"					
Localized	vs.	None	-0.42 (-1.40, 0.56)	-0.53 (-1.52, 0.46)	-0.30 (-1.26, 0.66)
Multi-systemic	vs.	None	-0.80 (-3.45, 1.86)	-0.90 (-3.48, 1.68)	0.25 (-2.42, 2.91)
ATT weighted to match "Localized"					
None	vs.	Localized	0.47 (-0.61, 1.55)	0.68 (-0.39, 1.74)	0.21 (-0.16, 0.58)
Multi-systemic	vs.	Localized	-0.77 (-3.62, 2.08)	-0.43 (-3.10, 2.24)	-0.05 (-1.07, 0.98)
ATT weighted to match "Multi-systemic"					
None	vs.	Multi-systemic	0.88 (-1.54, 3.29)	0.65 (-1.76, 3.06)	0.16 (-2.29, 2.60)
Localized	vs.	Multi-systemic	0.68 (-1.91, 3.27)	0.23 (-2.34, 2.81)	0.03 (-2.60, 2.65)

Abbreviations: CL, confidence limit; ATE, average treatment effect; ATT, average treatment effect among treated.

† Differences are calculated as 1st group - 2nd group, where pairs are expressed as "1st group vs. 2nd group."

Table 3.9.7 Mean intelligence quotient (IQ) estimates at age 7 by gestational timing of multi-systemic bacterial infection.

			Full-Scale IQ	Verbal IQ	Performance IQ
			ΔMean (95% CLs)†	*ΔMean (95% CLs)*†	*ΔMean (95% CLs)*†
Unweighted analyses					
1st	vs.	None	-1.56 (-4.75, 1.63)	-0.93 (-4.06, 2.2)	-2.52 (-5.71, 0.67)
2nd	vs.	None	-1.63 (-4.76, 1.49)	-1.70 (-4.77, 1.37)	-1.51 (-4.63, 1.62)
3rd	vs.	None	-7.40 (-10.35, -4.44)	-6.41 (-9.35, -3.47)	-5.86 (-8.86, -2.86)
2nd	vs.	1st	-0.07 (-4.22, 4.07)	-0.77 (-5.11, 3.58)	1.01 (-3.35, 5.38)
3rd	vs.	1st	-5.84 (-9.88, -1.80)	-5.48 (-9.58, -1.38)	-3.34 (-7.86, 1.18)
3rd	vs.	2nd	-5.76 (-9.64, -2.04)	-4.71 (-8.68, -0.75)	-4.35 (-8.71, 0.01)
ATE weighted analyses					
1st	vs.	None	-1.00 (-4.15, 2.15)	-0.50 (-3.66, 2.67)	-1.94 (-5.21, 1.34)
2nd	vs.	None	-1.46 (-4.26, 1.35)	-1.50 (-4.42, 1.43)	-1.25 (-4.29, 1.80)
3rd	vs.	None	-4.45 (-7.09, -1.81)	-4.13 (-6.85, -1.41)	-3.25 (-6.10, -0.40)
2nd	vs.	1st	-0.46 (-4.66, 3.74)	-1.00 (-5.29, 3.29)	0.69 (-3.76, 5.14)
3rd	vs.	1st	-3.45 (-7.54, 0.64)	-3.63 (-7.79, 0.52)	-1.31 (-5.63, 3.01)
3rd	vs.	2nd	-2.99 (-6.82, 0.84)	-2.63 (-6.60, 1.34)	-2.00 (-6.15, 2.15)
ATT weighted to match "None"					
1st	vs.	None	-1.01 (-4.16, 2.14)	-0.51 (-3.67, 2.66)	-1.95 (-5.22, 1.33)
2nd	vs.	None	-1.50 (-4.36, 1.35)	-1.84 (-4.80, 1.12)	-1.00 (-4.14, 2.15)
3rd	vs.	None	-4.31 (-6.96, -1.66)	-4.09 (-6.83, -1.35)	-3.08 (-5.91, -0.25)
ATT weighted to match "1st trimester"					
None	vs.	1st	1.13 (-2.00, 4.26)	0.34 (-2.85, 3.54)	2.27 (-0.95, 5.49)
2nd	vs.	1st	0.10 (-4.18, 4.38)	-0.25 (-5.11, 4.61)	0.69 (-3.66, 5.05)
3rd	vs.	1st	-3.81 (-8.14, 0.53)	-3.56 (-7.91, 0.78)	-1.62 (-6.20, 2.96)
ATT weighted to match "2nd trimester"					
None	vs.	2nd	0.93 (-1.84, 3.70)	1.00 (-1.99, 3.99)	0.91 (-2.08, 3.89)
1st	vs.	2nd	-1.07 (-5.60, 3.47)	-0.68 (-5.24, 3.88)	-1.72 (-6.68, 3.23)
3rd	vs.	2nd	-4.50 (-8.42, -0.57)	-4.21 (-8.17, -0.25)	-3.05 (-7.49, 1.38)
ATT weighted to match "3rd trimester"					
None	vs.	3rd	5.65 (3.00, 8.30)	4.49 (1.83, 7.15)	4.57 (1.39, 7.74)
1st	vs.	3rd	4.57 (0.59, 8.55)	4.18 (0.37, 7.99)	2.18 (-2.50, 6.86)
2nd	vs.	3rd	4.08 (0.35, 7.81)	2.73 (-1.61, 7.08)	3.41 (-0.72, 7.54)

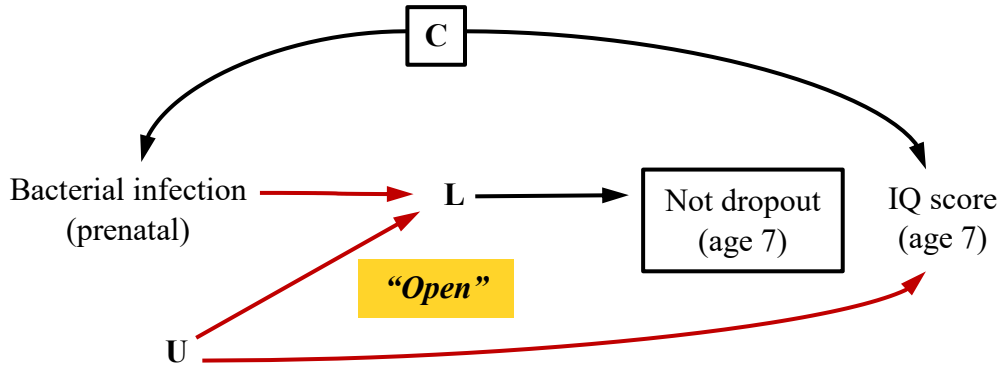
Abbreviations: CL, confidence limit; ATE, average treatment effect; ATT, average treatment effect among treated; 1st, first trimester; 2nd, second trimester; 3rd, third trimester.

† Differences are calculated as 1st group - 2nd group, where pairs are expressed as "1st group vs. 2nd group."

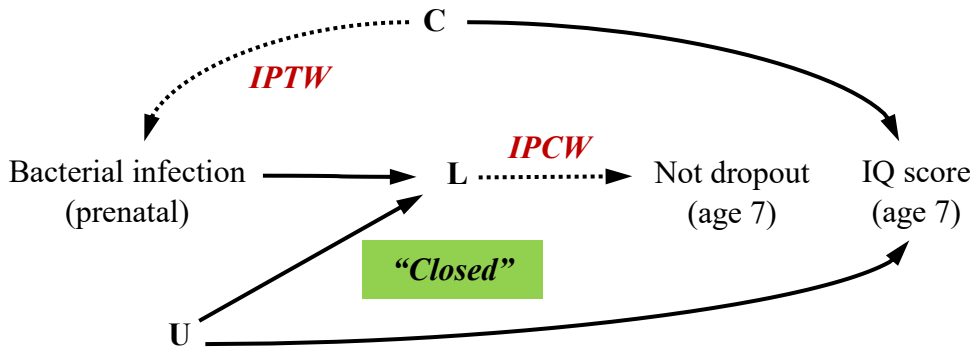
3.10 Supplementary Figures

Figure 3.10.1 Conceptual framework for inverse probability weighting: directed acyclic graphs (DAGs)

(a) Standard regression adjustment



(b) Inverse probability weighting



C: measured covariates, *U*: unmeasured covariates, *L*: any short-term outcomes of prenatal bacterial infection (e.g., preterm birth, low birthweight), *IPTW*: inverse probability weighting for treatment, *IPCW*: inverse probability censoring weighting.

Figure 3.10.2 Standardized effect size plots for estimating the propensity scores to generate inverse probability weights for severity of bacterial infection.

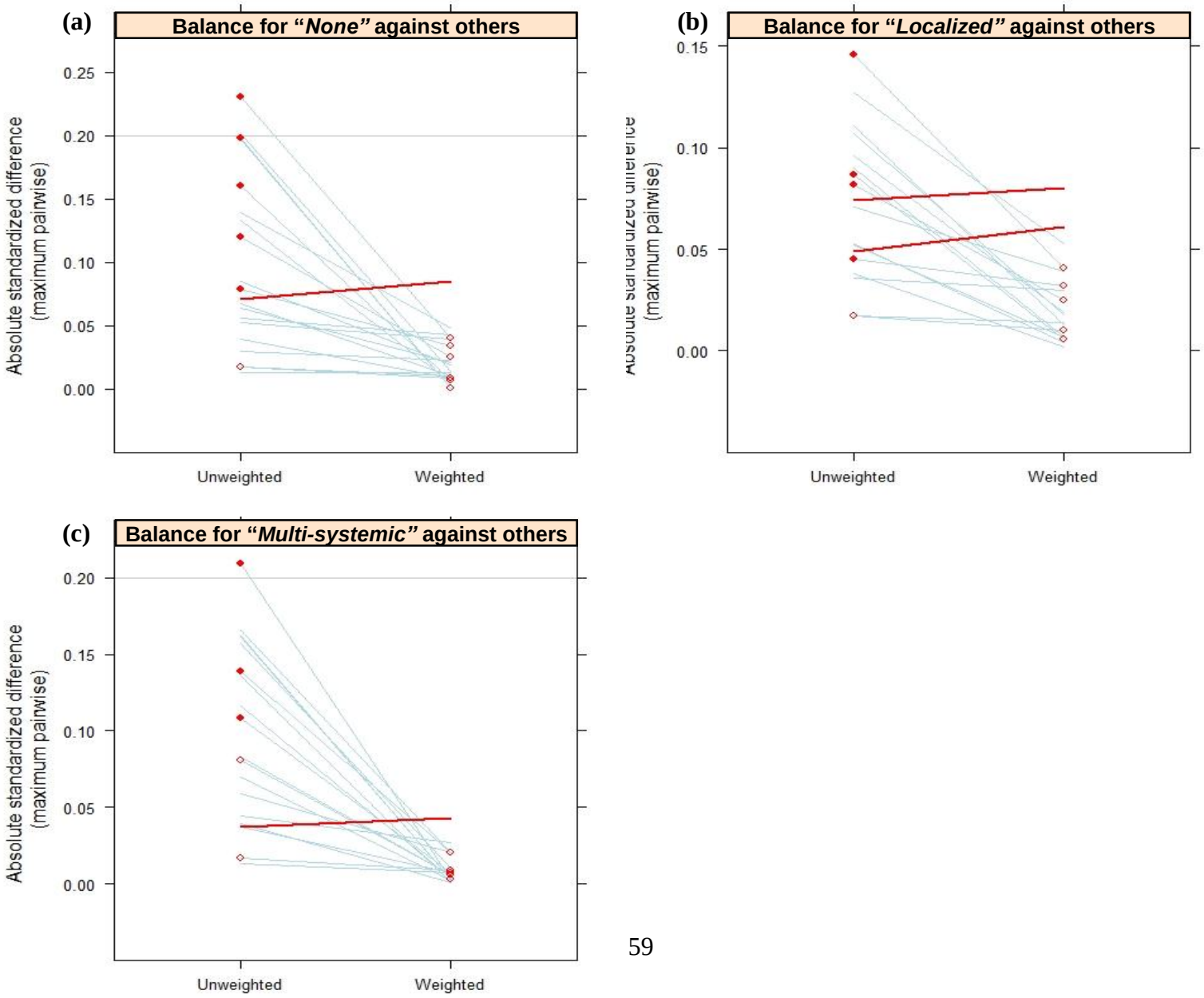
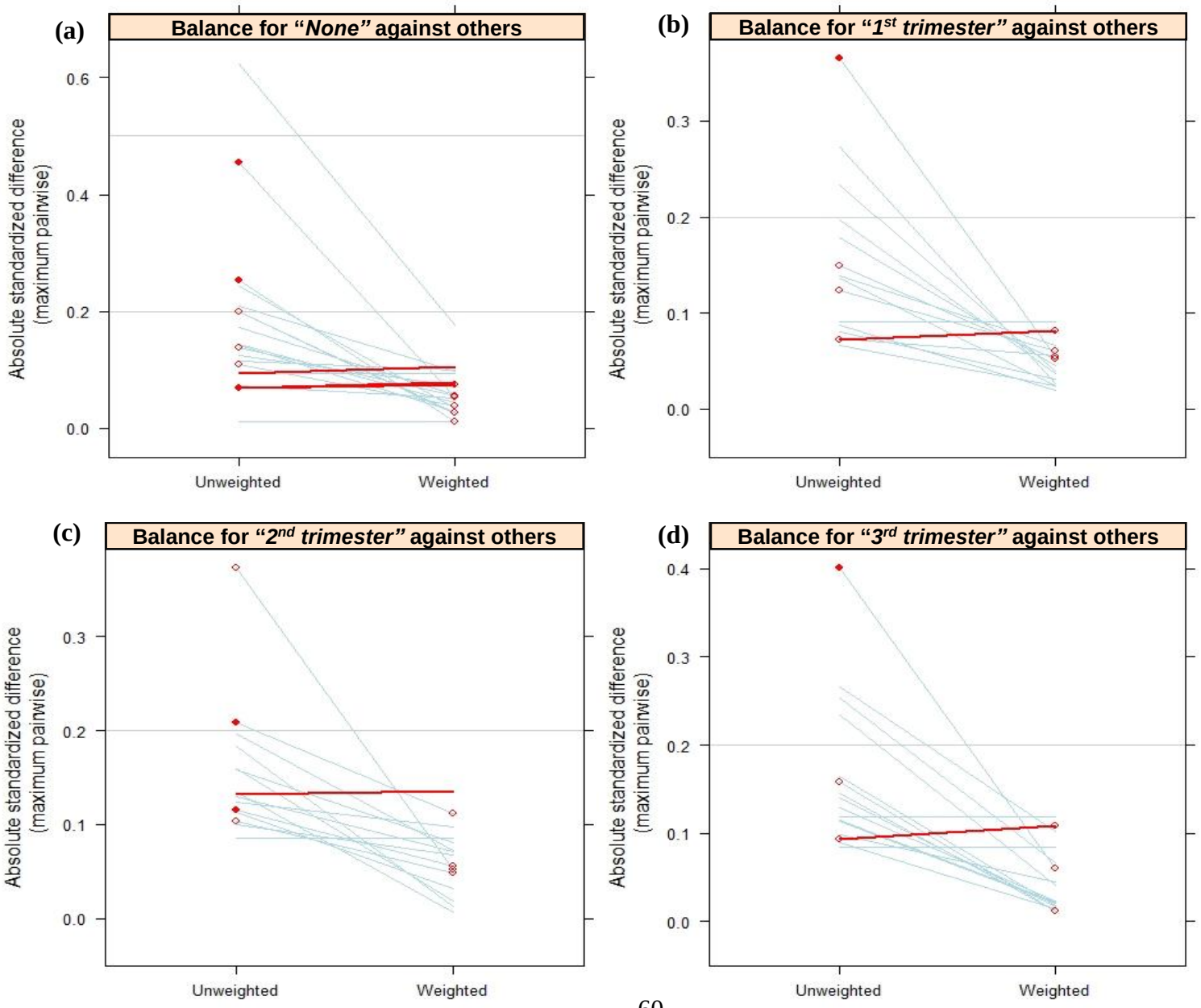


Figure 3.10.3 Standardized effect size plots for estimating the propensity scores to generate inverse probability weights for gestational timing of multi-systemic bacterial infection.



Chapter 4: Neurodevelopmental Impact of Prenatal Bacterial Infection on Memory Circuitry Structure in Early Midlife

4.1 Abstract

While there is an emerging body of literature suggesting an etiologic role of prenatal bacterial infection on psychosis risk in adulthood, limited attempt has been made to examine this link using neuroimaging data. Using structural magnetic resonance imaging scans, we aimed to explore variation in average gray matter volumes involved in working memory circuitry as a function of adult psychosis and prenatal bacterial infection. Subjects included 79 men and 89 women from the New England Family Study (NEFS) who were scanned using a high-resolution T1 sequence on a 1.5 T whole body scanner. Brain regions of interest (ROIs) included dorsolateral prefrontal cortex (DLPFC), hippocampus (HIPP), parahippocampus (paraHIPP), inferior parietal lobule (iPAR), superior parietal lobule (sPAR), and caudal anterior cingulate cortex (cACC). Using the Box's M test, we observed overall differences in the covariance matrices by adult psychosis and region-specific abnormalities in HIPP, paraHIPP, sPAR, and DLPFC among psychotic cases. We also found overall differences in covariance matrices by prenatal exposure to bacterial infection and region-specific abnormalities in HIPP, paraHIPP, and cACC. If replicated, these findings may suggest the potential role of subcortical volumetric abnormalities—involving HIPP and paraHIPP—in explaining the etiologic connection between prenatal bacterial infection and development of psychotic illness in adulthood.

4.2 Introduction

Previous studies have found structural changes throughout the brain in psychotic patients compared to non-psychiatric controls. Among these studies, volumetric abnormalities in brain regions involved in working memory function are among the most replicated structural anomalies found in schizophrenia research (116–118). Further, studies of individuals who are in the prodrome of schizophrenia also have identified multiple structural brain changes, suggesting that brain disturbances associated with the disorder may precede full disease occurrence and have neurodevelopmental origins (119,120). Despite these findings, few investigations have sought to examine the contributions of environmental risk factors to neuroanatomic abnormalities found in schizophrenia.

Among the possible environmental contributors, maternal infection during pregnancy has been repeatedly linked to an elevated risk for schizophrenia and related psychoses in adulthood (11), with a growing recognition of the etiologic role of bacterial infection (30,31,81). However, limited effort has been made to explore the suggested link between prenatal immune challenges and psychosis risk using neuroimaging data (121). For example, Ellman and colleagues found that fetal exposure to elevated levels of pro-inflammatory cytokine (e.g., interleukin-8) predicted significant structural alterations among schizophrenia cases but not among healthy controls. Like many other neurobiological studies, they examined volumetric abnormalities in individual brain regions rather than a network of brain regions (122).

The focus has shifted to the interactions between specific brain areas and more recently to the possibility of a global pathology affecting connections across the brain. Several methods for structural imaging have been proposed to investigate associations between regions within and between brain networks (17,18). Among them, techniques based on covariance modeling have

been found to be particularly useful in several brain disorders (19–27). Included in this literature were publications of our group that investigated differences in the covariance of regions within working memory circuitry by schizophrenia (123), and more recently, by sex and reproductive status (29). In the present study, I examined covariation between the same brain regions assessed in these studies using a "Box's M test" (124). An underlying assumption in this analytic method is that morphometric features of brain regions within the subjects are correlated with each other due to shared neurodevelopmental and functional processes. While cortical thickness would be a more sensitive measure to gyral level differences (125), I studied gray matter volume in order to examine subcortical structures such as hippocampus and parahippocampus.

Lastly, most neuroimaging studies concerning schizophrenia and other psychotic disorders have drawn participants from the treated population that may not be representative of the general population (126). Only a few existing imaging studies, such as that of Cannon et al. (123) and Ellman et al. (121,127) have used epidemiologically principled population-based strategies to select study participants. In the present study, I aimed to explore whether there are volumetric abnormalities associated with prenatal infection that are known or suspected to be related to psychosis using a population-based sample of men and women in early midlife. Based on our group's previous work (81), I hypothesized that the network of brain regions supporting working memory function would differ significantly by adult psychosis and prenatal bacterial infection. In addition, I sought to identify volumetric abnormalities in specific brain regions that would drive the overall differences detected by the Box's M test. Volumetric alterations that are jointly displayed by individuals with psychosis and those prenatally exposed to bacterial infection might suggest their potential role in explaining the relationship between the two conditions (30,81).

4.3 Methods

4.3.1 Description of the Cohort

Participants were selected from 17,741 pregnancies that constitute the New England Family Study (NEFS), a Boston-Providence subsidiary of the Collaborative Perinatal Project. The NEFS is a prospective study initiated over 50 years ago to investigate prenatal and familial antecedents of pediatric, neurological, and psychological disorders of childhood (45). Pregnant women, recruited between 1959 and 1966, were representative of patients receiving prenatal care in the Boston-Providence area. Many types of assessments, including psychological examinations, were conducted on offspring up to 7 years of age, when the study officially ended in 1973. In a series of studies over the last 20 years, we followed the offspring of these pregnancies to investigate the fetal programming of adult phenotypes and sex differences therein. The current study investigated the fetal programming of adult psychosis and potential role of structural abnormalities in early midlife. The NEFS offspring were recruited at the time of 46-53 years of age and completed clinical, cognitive, and neuropsychological assessments and functional and structural magnetic resonance imaging (fMRI/SMRI/DTI).

4.3.2 Ascertainment of Adult Psychosis

Adult offspring with major non-organic psychoses (including schizophrenia, schizoaffective disorder, delusional disorder, brief psychosis, psychosis NOS, bipolar disorder with psychotic features, and major depressive disorder with psychosis) within NEFS cohorts were identified approximately 30 years later through a two-stage diagnostic assessment procedure between 1996 and 2007. The investigators were blind to prior assessments of these subjects during this follow-up. NEFS parents and offspring with a 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 NEFS cohort, involving direct interviews with approximately 20% of the cohort; and (c) reports from participants in these interview studies of a family member with a history of psychotic or bipolar symptoms or diagnosis. Controls were selected from families participating in the control arm of a NEFS high-risk study in which the control population was a random stratified sample of parents selected from the entire NEFS cohort, with no known history of psychosis or other major Axis I disorders. Thus, the NEFS sample of psychotic cases and controls is a representative community sample of subjects.

4.3.3 Ascertainment of Prenatal Exposure to Bacterial Infection

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 (49). 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 and medically edit 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 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 all available

hospital records no later than 6 months after termination of a given pregnancy. In the current study, we included all 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.

4.3.4 Inclusion and Exclusion Criteria

Exclusion criteria for all adult participants were a history of neurological disease, traumatic brain injury, medical illness or alcohol-related disease with documented cognitive sequelae, major sensory impairments (e.g. deafness), IQ<65 in adulthood or inability to understand the procedures, <6 years of formal education and severe substance abuse within the past 6 months (128). All psychotic cases were living in the community when assessed. On the other hand, controls had to be free of any known lifetime history of psychosis or other major Axis I disorders, and their parents, parents' siblings, and grandparents had to be free of any known lifetime history of psychosis, bipolar, schizotypal, recurrent MDD, suicide attempts or psychiatric hospitalizations.

From the NEFS, 114 psychotic cases were identified through the case ascertainment procedure described in Section 4.3.2. As depicted in Figure 4.3.1, structural MRI scans were collected from a total number of 179 participants through four case-control MRI studies (129–132). In the current study, three subjects were excluded given an incomplete or noisy T1-weighted scan, and additional eight subjects were excluded given missing information on prenatal exposure to bacterial infection. The goal of the current case-control study was to explore altered volumetric connections in working memory circuitry in relation to adult psychosis and prenatal bacterial infection. I conducted two separate sets of analyses in which I divided the final sample of 168 participants into two groups based on psychosis status (case vs. control) and exposure status (exposed vs. unexposed), respectively. In each set of analyses, I explored if

patterns of overall covariances and region-specific correlations differed between the two groups being compared. Human subjects' approval was granted by Partners Health Care and Brown University. All volunteers gave written informed consent and were paid for their participation.

4.3.5 Regions of interest (ROIs)

We restricted the network to areas that demonstrate: (a) involvement in working memory across all tasks and methods found in a PubMed (National Center for Biotechnology Information, U.S. National Library of Medicines, Bethesda, Maryland) search of studies reviewing the use of representative methods for studying the cognitive neuroscience of memory (133–147); (b) anatomical abnormalities found in schizophrenia (117,118,148–151). These criteria yielded a network of hippocampus (HIPP), parahippocampus (paraHIPP), superior parietal cortex (sPAR), inferior parietal cortex (iPAR), caudal anterior cingulate cortex (cACC), and dorsolateral prefrontal cortex (DLPFC) regions.

4.3.6 Structural Magnetic Resonance Imaging

The analytic sample including 168 participants consists of four sub-samples, which originate from four case-control MRI studies of the NEFS. For a first sub-sample including 76 participants, T1-weighted structural scans (TE = 3.31ms; TI = 1000ms; TR = 2730ms; Flip angle = 7°; FOV = 25.6cm; Spatial resolution = 1.0 x 1.0 x 1.33mm; matrix = 256 x 256mm; Slice acquisition direction = sagittal) were acquired on a 1.5 Tesla Siemens Avanto scanner using a 4-channel head coil. For a second sub-sample including 65 participants, T1-weighted structural scans (TE = 3.39ms; TI = 1000ms; TR = 2730ms; Flip angle = 7°; FOV = 25.6cm; Spatial resolution = 1.0 x 1.0 x 1.33mm; matrix = 256 x 256mm; Slice acquisition direction = sagittal) were collected on a 1.5 Tesla Siemens Sonata scanner using a CP coil. For a third sub-sample including 23 participants, T1-weighted structural scans were acquired also on a 1.5 Tesla

Siemens Sonata scanner (TE = 4.3ms; TI = 8ms; TR = 11.8ms; Flip angle = 8°; FOV = 25.6cm; Spatial resolution = 1.0 x 1.0 x 1.5mm; matrix = 256 x 256mm; Slice acquisition direction = sagittal, CP head coil). For a fourth sub-sample including 4 participants, T1-weighted structural scans were collected on a 1.5T GE Genesis Signa scanner (TE = 1.6ms; TI = 300ms; TR = 6.7ms; Flip angle = 25°; FOV = 24cm; Spatial resolution = 0.94 x 0.94 x 1.5mm; matrix = 256 x 256mm; Slice acquisition direction = sagittal, CP head coil).

Images were checked visually for possible movement artifacts. To correct for head tilt, each MRI scan was realigned, horizontally to the anterior commissure-posterior commissure line, and vertically to the sagittal sulcus. Automatic brain masking was conducted using Multi Atlas Brain Segmentation (152). Segmentation of the scans was executed using FreeSurfer 5.3 (153), and quality of segmentations was determined by visual inspection. Based on visual inspection, all FreeSurfer segmentations were included in further analysis. Gray matter volumes for memory circuitry (HIPP, paraHIPP, iPAR, sPAR, rACC, and DLPFC) were calculated using FreeSurfer segmentation. Regarding the hippocampus, HIPP represents a conservative definition of the hippocampal formation as per Caviness, Meyer, Makris, and Kennedy (17) and Makris et al. (154), including cornu amonis, dentate gyrus, subiculum, presubiculum, and parasubiculum (but not the entorhinal cortex), a terminology that has been adopted by the FreeSurfer parcellation system (153).

4.3.7 Statistical Analyses

To explore abnormal volumetric connections within working memory circuitry, I employed a three-stage analytic approach. In the first stage, I compared covariance matrices by (a) psychosis status and (b) prenatal bacterial infection using Box's M test which tests for the equality of covariance matrices between groups. If there were significant or borderline

significant overall differences in Box's M test, I moved on to the second stage in which I compared pairwise correlation coefficients among the six ROIs; the goal of this analysis was to identify specific regions that might have contributed to the overall differences in the Box's M test. In the final stage of analysis, I compared the list of pairwise correlations and identified the regions that were jointly implicated in prenatal bacterial infection and adult psychosis. In the main analysis, I examined the effect sizes for average volume of the ROIs. To explore potential lateralization of structural abnormalities, I additionally performed the same sets of analyses using hemisphere-specific volume of the ROIs.

Following Abbs et al. (28) and Seitz et al. (29), covariance patterns were analyzed between predefined working memory networks (i.e., HIPP, paraHIPP, iPAR, sPAR, rACC, and DLPFC), and covariance structures were compared between groups. I first compared those with psychosis against those without. Following this, I compared those prenatally exposed to bacterial infection and those unexposed. For comparison of covariance patterns, I employed the Box's M test using the following statistic (124,155):

$$M = (n - T)\ln|C| - \sum_{i=1}^{T}(n_i - 1)\,|C_i|$$

$$C = \frac{1}{n - T}\sum_{i=1}^{T}(n_i - 1)\,|C_i|$$

where C_i is the variance-covariance matrix calculated from the group i, T is the number of subgroups for which equality of matrices is tested, and n_i is the sample size of each group i.

The Box's M test statistic can be approximated by an *F* statistic, whereas the rejection of the null hypothesis on a significance level of $p < 0.05$ is interpreted as the overall covariance pattern between two groups being different from one another. The Box's M tests allow for the

comparison of covariance matrices, rather than looking at single brain volumes or multiple correlations (and hence protects for issues of multiple comparison). If the Box's M test results were significant ($p < .05$) or trended toward significance ($p < .10$), correlation coefficients for each pair of regions of interest (ROIs) between the two groups were compared. I would argue that the more liberal threshold of $p < .10$ for trend significance is justified given that the Box's M test already protects against multiple comparison errors. Furthermore, a more liberal threshold also protects against Type II error, likely to occur in correlation comparisons with rather small sample sizes.

In cases where Box's M test results are significant, it is still unclear whether they represent differences in correlations, differences in variances, or both. To address this issue, I additionally employed the Jennrich (*J*) test using the following formula (156):

$$J = \sum_{i=1}^{m} \left\{ \frac{1}{2} tr(Z_i^2) - (Z_d)' W^{-1} Z_d \right\}$$

where $Z_i = \sqrt{n_i} \bar{R}^{-1} (R_i - \bar{R})$, R_i is the *i*-th sample correlation, $\bar{R}$ is the average of all sample correlation matrices, $W = I_p + \bar{R} * \bar{R}^{-1}$ (* is the Hadamard product of two matrices), Z_d is a diagonal of Z_i, and I_p is the identity matrix of size $(p \times p)$.

Correlation coefficients were converted to a normal distribution using Fisher's Z transformation, and Z values were used to test for differences between groups. Additionally, given the relatively low number of participants in each group, bootstrapping (number of iterations = 100,000, 95% bias-corrected accelerated confidence intervals) was performed for these correlation coefficients (157,158). Bootstrapping is a method to assign accuracy to sample estimates by resampling with replacement from the original data. By looking not only at single value (in this case correlation coefficient) but rather at a confidence interval, one can control and

check the stability of original results. All statistical analyses were conducted using R version 3.5.3 (159).

It has sometimes been assumed in brain volumetric studies that deviations in regional brain size in clinical samples are directly related to abnormal neurodevelopment or pathogenesis. However, this assumption may be incorrect as it is often unclear to what extent such volumetric differences may be attributable to individual differences in overall dimension (e.g., head circumference, body size, brain volume). There are three most commonly used statistical methods to adjust for allometric contributors to volume differences (160): the *proportion, generalized linear models-analysis of covariance (GLM/ANCOVA),* and *residual* approaches. The *proportion* approach uses as its numerator the volume of an ROI for an individual and as its denominator a volumetric measure of brain size of that individual (e.g., volume of total brain or of some large structure of which the ROIs are components); volume is not expressed as a quantity (e.g., cubic centimeters), but a ratio, fraction, or proportion. The *GLM/ANCOVA* approach adopts the raw volume of an ROI as the outcome variable and analyzes it using a linear regression model with relevant covariates as predictors. In the *residual* approach, the raw ROI volume is regressed on the intracranial volume as well as other covariates (161). The predicted volumes are subtracted from the observed volumes for each subject in the dataset. The resulting values are the residuals for each subject, which represent the deviation of an individual subject's volume from the ROI volume predicted using the subject's specific values for each covariate (e.g., age, sex, intracranial volume). While the *proportion* and *GLM/ANCOVA* methods are more widely used than the *residual* method, Mathalon et al. (162) argues that the former is inherently less reliable because a proportion has two sources of measurement error: one from the numerator measure (i.e., ROI volumes) and the other from the denominator measure (i.e., intracranial

volume). Therefore, in the current study, all ROI volumes were corrected for total intracranial volume (ICV) as well as relevant covariates using the residual approach. The covariates included offspring's sex, offspring's year of birth, offspring's age at MRI scan, study site, maternal race/ethnicity, parental socioeconomic index, and length of maternal education.

4.4 Results

4.4.1 Sample Demographics

Summary statistics on demographic and clinical characteristics are tabulated in Table 4.7.1 and Table 4.7.2. Participants in psychotic and control groups were well matched in terms of offspring sex, maternal race/ethnicity and education, season of birth, parental history of mental illness and socioeconomic status, and age at MRI scan. With respect to prenatal exposure to bacterial infection, exposed mothers were significantly more likely to be non-white than unexposed mothers. Participants in the exposed and unexposed groups were comparable in terms of offspring sex, study site, season of birth, maternal education, parental socioeconomic index, and age at MRI scan.

4.4.2 Descriptive Results: Hippocampal and Parahippocampal Volume

There was evidence for significant lateralization of hippocampal and parahippocampal volumes. Right hippocampus was generally larger than left, whereas left parahippocampus was larger than right (seeSupplementary Table 4.9.3). When we compared volumetric differences by adult psychosis and offspring sex, male cases had significantly smaller hippocampus than did male controls and female cases. On the other hand, male controls had significantly larger hippocampus and slightly smaller parahippocampus than did female controls. With respect to prenatal exposure to bacterial infection, exposed individuals had larger hippocampus compared to those unexposed, especially in the right hemisphere. However, these volumetric differences

did not reach the level of statistical significance. This finding was consistent with previous findings that fetal exposure to pro-inflammatory cytokine is associated with greater hippocampal size in the right hemisphere (121).

4.4.3 Analytic Results: Adult Psychosis

Analysis of mean volumes. Comparison of covariance matrix of the working memory circuitry using the Box's M test (124) trended toward significant differences by adult psychosis (χ^2 = 30.90, *df* = 21, *p* = 0.08). These results were replicated using the Jennrich's test (seeSupplementary Table 4.9.1). Posthoc analyses of the correlation coefficients comparing individuals with psychosis and those without revealed that overall covariance differences by adult psychosis were driven by differences in three relationships involving HIPP, paraHIPP, DLPFC, and sPAR (see Table 4.4.3 and Figure 4.8.3). Psychotic cases showed moderate positive correlations involving these regional volumes while controls did not.

Analysis of hemisphere-specific volumes. We observed statistically significant differences in the right hemisphere (χ^2 = 39.46, *df* = 21, *p* = 0.01) by psychosis status, but no significant differences in the left hemisphere (χ^2 = 24.70, *df* = 21, *p* = 0.26). These results were also replicated using the Jennrich's test (seeSupplementary Table 4.9.1). In the exploratory analyses of the correlation coefficients in the right hemisphere, we found that overall covariance differences by adult psychosis were driven by differences in two relationships involving HIPP, paraHIPP, and iPAR (seeSupplementary Table 4.9.4). Among psychotic cases, the average volume of iPAR showed a strong negative correlation with that of paraHIPP and a moderate positive correlation with the volume of HIPP.

4.4.4 Analytic Results: Prenatal Exposure to Bacterial Infection

Analysis of mean volumes. Comparison of covariance matrix of the working memory circuitry trended toward significant differences by prenatal bacterial infection (χ^2 = 31.70, *df* = 21, p = 0.06). These results were replicated using the Jennrich's test (seeSupplementary Table 4.9.1). Posthoc analyses of the correlation coefficients comparing exposed individuals and those unexposed revealed that overall covariance differences were driven by two relationships involving HIPP, paraHIPP, and cACC (and Figure 4.8.4). Exposed individuals showed moderate negative correlations involving these regional volumes, while controls did not.

Analysis of hemisphere-specific volumes. We observed significant differences by prenatal bacterial infection in the left hemisphere (χ^2= 40.09, *df* = 21, p = 0.01); however, the differences were no longer significant in the Jennrich's test (seeSupplementary Table 4.9.1). While the differences in the right hemisphere were marginally significant in the Box's M test (29.11, *df* = 21, p = 0.11), they reached the level of statistical significance in the Jennrich's test (χ^2 = 27.30, p = 0.03). In the exploratory analyses of the correlation coefficients in the right hemisphere, overall covariance differences by prenatal bacterial infection were driven by two relationships involving paraHIPP, sPAR, and DLPFC (seeSupplementary Table 4.9.5). Among exposed individuals, the volume of paraHIPP showed a moderate positive association with that of sPAR and a strong negative association with the volume of DLPFC, whereas unexposed individuals did not.

4.5 Discussion

Covariance analysis assumes that brain areas of a functional network are connected through shared neurodevelopmental processes (28), and thus, suitable to analyze the regions as a *network*, as distinct from independent regions. Using this method, I explored volumetric

abnormalities within working memory circuitry and the co-relationships, or *covariances*, in early midlife in relation to adult psychosis and prenatal bacterial infection. In this case-control study, covariance patterns in working memory circuitry regions significantly differed comparing (a) psychotic cases and controls, and (b) exposed and unexposed. These findings may imply the potential role of structural abnormalities within working memory circuitry in the etiologic link between prenatal bacterial infection and adult psychosis.

While these analyses are not traditionally thought of as a connectivity analysis, brain regions studied in the current study are known to have direct or indirect anatomical connections (142,163). For example, HIPP is connected with iPAR and DLPFC (164) as well as with ACC (165,166). Additionally, iPAR is directly connected with DLPFC and ACC (146,167), and paraHIPP is connected with HIPP and other cortical areas (146). Since the HIPP provides important input to the DLPFC (142) and because neonatal HIPP lesions induce post-pubertally manifested changes in prefrontal cortex (173) mimicking aspects of schizophrenic pathophysiology, it has been hypothesized that the interaction between these two regions might be particularly disturbed in this disorder (174–176). While it is highly implausible that this complex and heterogenous disorder can be reduced to a single causal chain, this formation may help guide further research in suggesting a study of impaired HIPP-DLPFC interactions in individuals with schizophrenia and preclinical models of this disorder.

It is also becoming evident that persons suffering from depression and post-traumatic stress disorder display structural brain anomalies and aberrant functional coupling within the HIPP-DLPFC circuit (177). Considering that these disorders involve varying degrees of cognitive impairment and emotional dysregulation, dysfunction in the HIPP-DLPFC pathway might therefore be the common element of their pathophysiology (178,179). In consequence, the

HIPP- DLPFC pathway is a potentially crucial element of the pathophysiology of several psychiatric diseases, and it offers a specific target for therapeutic intervention, which is consistent with the recent emphasis on reframing psychiatric diseases in terms of brain circuits.

In the current study, individuals prenatally exposed to bacterial infection displayed alterations in volumetric connections involving HIPP and paraHIPP—potentially suggesting their neurodevelopmental origins. These findings are consistent with previous literature that subcortical structures including HIPP and paraHIPP are particularly vulnerable to both genetic and environmental insults occurring during the perinatal period (180,181) including pregnancy complications (182), infection (183), and stress (184). For instance, it has been suggested that early developmental insults to the hippocampus might lead to impaired connections between HIPP and DLPFC. They might also induce maturational deficits in DLPFC circuitry and ultimately DLPFC dysfunction, which accounts for the core neuropsychology of several psychiatric disorder including, but not limited to, psychosis.

Alternatively, it is also possible that early insults to paraHIPP could secondarily affect HIPP. For example, a disturbed architecture of entorhinal cortex neurons could lead to abnormal connections with HIPP (186), as in Alzheimer's disease (187,188), and some form of epilepsy (112), in which the initial pathology is located in the parahippocampal subregions. Given that psychotic cases in the present study also displayed region-specific abnormalities in HIPP and paraHIPP, the findings may offer a potential explanation for epidemiologic evidence linking psychotic disorders to early neurodevelopmental disturbances. Nevertheless, it remains unclear how much clinical significance these findings may have given the modest effect sizes. Future investigations incorporating data on cognitive test performance (e.g., California Verbal

Language Test Trial 5) would help elucidate the functional significance of the differences in covariance among working memory regions observed in the present study.

There were several limitations in the present study that should be noted. Given the multiple tests conducted in this study, it is possible that spurious findings arose from Type I error. It appears unlikely, however, that our results are entirely due to chance, as they are consistent with many previous studies in clinical and preclinical studies of schizophrenia. Nevertheless, we have used the Box's M test which allows for protection of multiple testing for the simple correlations. The weak power associated with a modest sample size indicated the possibility of Type II error. Therefore, we adjusted the threshold to protect against this error in order to view any trends in the data; however, threshold selection ultimately did not impact the main findings involving HIPP and paraHIPP.

To operationalize the degree of linkage between brain regions, our study employed structural connectivity—which is based on covariance. Limitations arise because neuronal interactions need not be linear, and linear correlation does not imply causality. However, much neuroimaging evidence suggests that linear correlations do capture an important aspect of neuronal interactions across different scales. It would be of interest to extend the present data using analytic methods that allow the investigation of directional interactions and models of causal relationships—such as effective connectivity (191).

In addition, the sample was limited to slightly more than 22% of 116 psychotic cases identified in the original NEFS cohort, raising the potential for selection bias. However, psychotic cases who participated in the MRI study and cases who did not participate did not differ with regard to several demographic variables and prenatal exposure to bacterial infection (see Table 4.9.2). Therefore, it is unlikely that case ascertainment bias accounts for our findings.

Bias would be also mitigated by the fact that the sample was derived from the population-based study, in contrast to many clinical imaging studies that draw upon hospital or clinic-based samples.

Like most existing neuroimaging studies of psychotic disorders, our study was also cross-sectional in design. However, as with detecting dementia, it is possible that structural brain change over time could be one of the most important indicators of impending onset of psychosis. For example, Pantelis et al. (120) compared volumetric changes in frontal, temporal, and parietal gray matter before and after the onset of psychosis and found significant reduction among participants who transitioned to psychosis but not among those who did not. These findings have been replicated by Borgwardt et al. (192) and substantiated by Prasad et al. (193) that also considered the putative effects of immune activation on the longitudinal changes in gray matter volumes. Thus, future studies are encouraged to collect multiple scans over time and monitor the neuroanatomic changes to better inform the underlying mechanism for these changes and assess their utility as potential metrics for the development of psychosis.

4.6 Conclusions

There were overall covariance differences by adult psychosis and prenatal bacterial infection in average volumes of six brain regions supporting working memory functions. Posthoc analyses of region-specific correlations indicated that the overall differences by the two conditions might be primarily attributable to the altered anatomical connections involving hippocampus and parahippocampus. If replicated, this may suggest the potential roles of subcortical volumetric abnormalities in explaining the link between prenatal immune challenges and adult psychosis.

4.7 Tables

Table 4.7.1 Demographic characteristics by offspring sex and adult psychosis status.

		Male		Female		
		Control	***Case***	***Control***	***Case***	***p***
Categorical variables, n (%)						
Sample size		64 (38.1)	15 (8.9)	79 (47.0)	10 (6.0)	
Maternal race/ethnicity	Non-white	3 (4.7)	2 (13.3)	6 (7.6)	2 (20.0)	.31
	White	61 (95.3)	13 (86.7)	73 (92.4)	8 (80.0)	
Study site	Boston	45 (70.3)	11 (73.3)	56 (70.9)	6 (60.0)	.90
	Providence	19 (29.7)	4 (26.7)	23 (29.1)	4 (40.0)	
Season of birth	Summer-Fall	46 (71.9)	13 (86.7)	59 (74.7)	7 (70.0)	.68
	Winter-Spring	18 (28.1)	2 (13.3)	20 (25.3)	3 (30.0)	
Prenatal bacterial infection	Exposed	14 (21.9)	5 (33.3)	12 (15.2)	1 (10.0)	.31
	Unexposed	50 (78.1)	10 (66.7)	67 (84.8)	9 (90.0)	
Parental mental illness	Present	19 (29.7)	2 (13.3)	23 (29.1)	1 (10.0)	.35
	Absent	45 (70.3)	13 (86.7)	56 (70.9)	9 (90.0)	
Continuous variables, mean (sd)						
Birth year		1962.6 (1.9)	1962.3 (2.4)	1962.6 (2.0)	1963.2 (1.9)	.72
Maternal education		11.5 (2.4)	11.0 (2.3)	11.5 (2.2)	11.9 (1.7)	.80
Parental socioeconomic status		5.8 (1.3)	5.7 (1.1)	5.7 (1.0)	4.8 (2.4)	.13
Age at MRI scan		41.6 (3.6)	41.6 (4.2)	42.0 (3.1)	40.4 (3.1)	.56

Abbreviations: MRI, magnetic resonance imaging.

Table 4.7.2 Demographic characteristics by prenatal exposure to bacterial infection.

		Prenatal bacterial infection		
		Unexposed	***Exposed***	***p***
Categorical variables, n (%)				
Sample size		136 (81.0)	32 (19.0)	
Sex	Female	76 (55.9)	13 (40.6)	.17
	Male	60 (44.1)	19 (59.4)	
Maternal race/ethnicity	Non-white	7 (5.1)	6 (18.8)	.03
	White	129 (94.9)	26 (81.2)	
Study site	Boston	98 (72.1)	20 (62.5)	.40
	Providence	38 (27.9)	12 (37.5)	
Season of birth	Summer-Fall	102 (75.0)	23 (71.9)	.89
	Winter-Spring	34 (25.0)	9 (28.1)	
Continuous variables, mean (sd)				
Birth year		1962.6 (2.0)	1962.6 (2.0)	.93
Maternal education		11.6 (2.3)	11.0 (2.2)	.19
Parental socioeconomic status		5.7 (1.2)	5.5 (1.5)	.47
Age at MRI scan		41.8 (3.5)	41.3 (3.1)	.44

Abbreviations: MRI, magnetic resonance imaging.

Table 4.7.3 Pearson correlation coefficients between average volumes of the regions of interest (ROIs) among psychotic cases and controls.

	Adult psychosis		
	Case	***Control***	***Test statistic***
Pearson correlation and 95% bias-corrected and accelerated (BCa) bootstrap confidence interval			
HIPP-paraHIPP	-.15 (-.57, .27)	.10 (-.03, .21)	Z = 1.10, p=.27
HIPP-sPAR	.19 (-.24, .67)	-.14 (-.28, .01)	Z = 1.45, p=.15
HIPP-iPAR	-.24 (-.65, .25)	.11 (-.06, .29)	Z = 1.55, p=.12
HIPP-cACC	-.27 (-.64, .09)	.06 (-.10, .20)	Z = 1.45, p=.15
HIPP-DLPFC	**.37 (.03, .72)**	**-.12 (-.24, .01)**	**Z = 2.19, p=.03**
paraHIPP-iPAR	-.39 (-.58, -.10)	-.06 (-.18, .07)	Z = 1.53, p=.13
paraHIPP-sPAR	**.37 (.00, .62)**	**-.07 (-.20, .06)**	**Z = 2.00, p=.05**
paraHIPP-cACC	-.21 (-.61, .41)	-.08 (-.24, .07)	Z = .55, p=.58
paraHIPP-DLPFC	**-.52 (-.70, -.27)**	**-.18 (-.31, -.03)**	**Z = 1.72, p=.09**
sPAR-iPAR	.23 (.04, .43)	-.11 (-.24, .04)	Z = 1.48, p=.14
sPAR-cACC	.24 (-.05, .48)	-.10 (-.27, .07)	Z = 1.52, p=.13
sPAR-DLPFC	**.39 (-.36, .85)**	**-.14 (-.31, .05)**	**Z = 2.41, p=.02**
iPAR-cACC	.17 (-.34, .63)	-.07 (-.22, .08)	Z = 1.08, p=.28
iPAR-DLPFC	-.19 (-.49, .13)	-.20 (-.31, -.07)	Z = .00, p=1.00
cACC-DLPFC	-.06 (-.42, .43)	.00 (-.12, .11)	Z = .26, p=.79

Abbreviations: HIPP, hippocampus; paraHIPP, parahippocampus; sPAR, superior parietal cortex; iPAR, inferior parietal cortex; cACC, caudal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex.

Table 4.7.4 Pearson correlation coefficients between average volumes of the regions of interest (ROIs) among exposed and unexposed individuals.

	Prenatal bacterial infection		
	Exposed	*Unexposed*	*Test statistic*
Pearson correlation and 95% bias-corrected and accelerated (BCa) bootstrap confidence interval			
HIPP-paraHIPP	.20 (-.18, .58)	.05 (-.07, .18)	Z = .74, p=.46
HIPP-sPAR	.03 (-.40, .46)	-.10 (-.22, .02)	Z = .66, p=.51
HIPP-iPAR	.05 (-.48, .65)	-.10 (-.28, .10)	Z = .75, p=.46
HIPP-cACC	**-.37 (-.69, -.05)**	**.07 (-.09, .22)**	**Z = 2.24, p=.03**
HIPP-DLPFC	-.19 (-.47, .25)	-.10 (-.26, .07)	Z = .44, p=.66
paraHIPP-iPAR	-.01 (-.30, .34)	-.12 (-.27, .01)	Z = .55, p=.58
paraHIPP-sPAR	.23 (-.03, .48)	-.09 (-.23, .05)	Z = 1.54, p=.12
paraHIPP-cACC	**-.41 (-.76, .10)**	**.03 (-.27, .27)**	**Z = 2.27, p=.02**
paraHIPP-DLPFC	-.22 (-.42, .07)	-.27 (-.42, -.08)	Z = .23, p=.82
sPAR-iPAR	.00 (-.41, .41)	-.09 (-.23, .07)	Z = .46, p=.64
sPAR-cACC	-.04 (-.29, .25)	-.13 (-.25, -.03)	Z = .48, p=.63
sPAR-DLPFC	-.26 (-.71, .18)	-.13 (-.34, .09)	Z = .68, p=.50
iPAR-cACC	.01 (-.33, .27)	-.12 (-.25, .01)	Z = .64, p=.52
iPAR-DLPFC	-.18 (-.51, .33)	-.20 (-.35, -.06)	Z = .09, p=.93
cACC-DLPFC	.12 (-.13, .32)	.01 (-.15, .15)	Z = .55, p=.58

Abbreviations: HIPP, hippocampus; paraHIPP, parahippocampus; sPAR, superior parietal cortex; iPAR, inferior parietal cortex; cACC, caudal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex.

4.8 Figures

Figure 4.8.1 Selection of analytic sample from the New England (NE) cohorts of the Collaborative Perinatal Project (CPP).

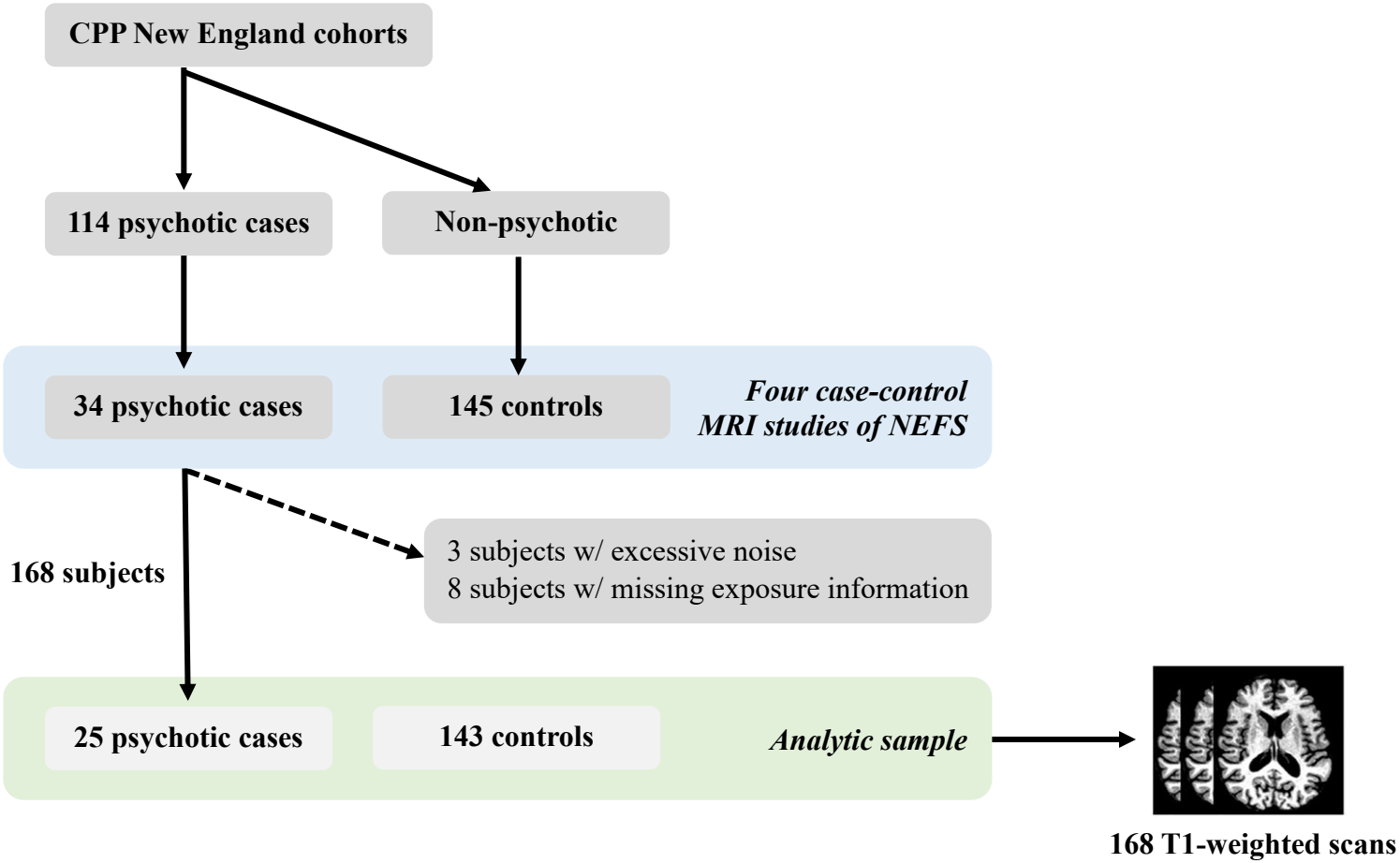


Figure 4.8.2 Schematic overview of analytical procedures.

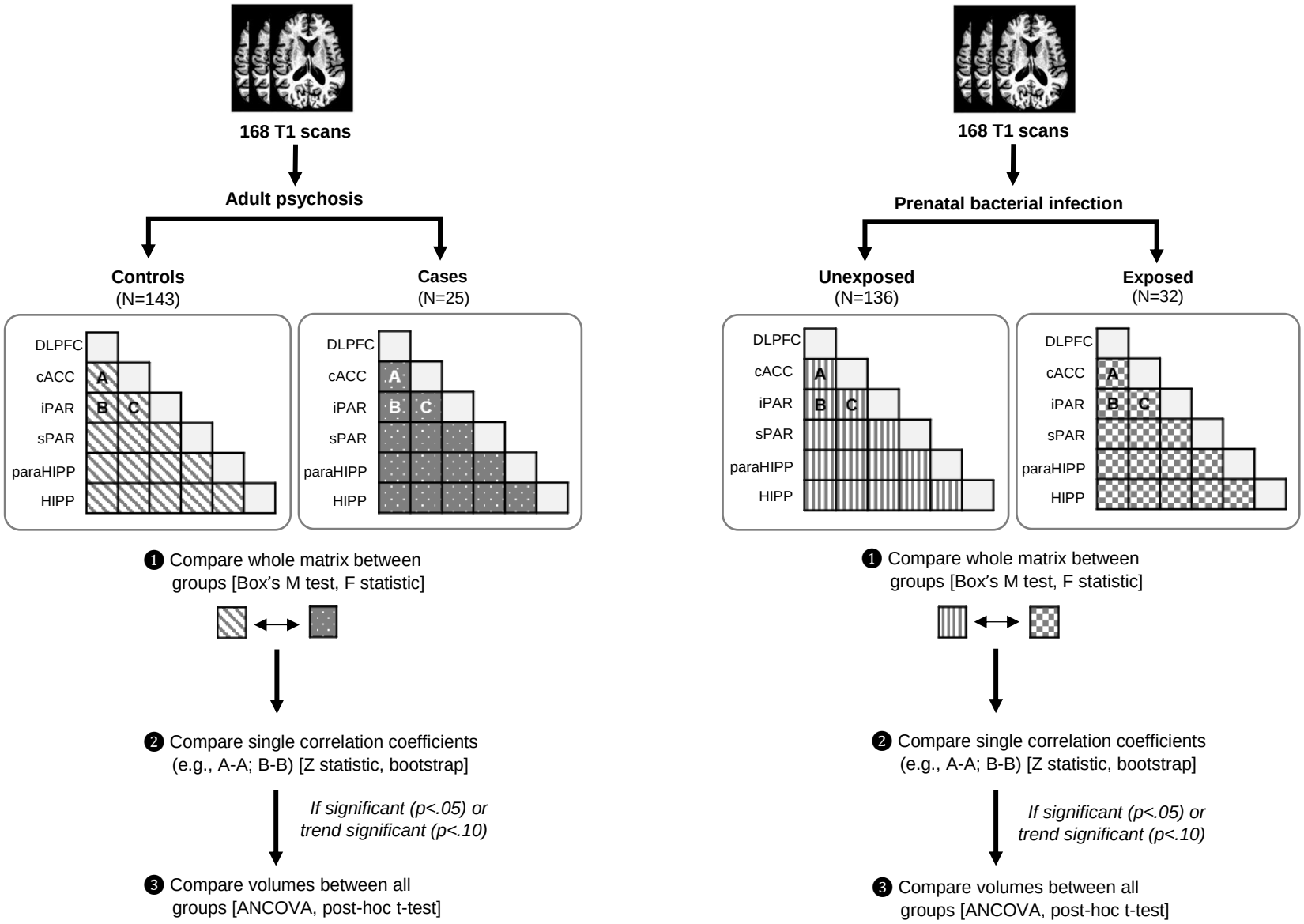


Figure 4.8.3 Associations between dorsolateral prefrontal cortex (DLPFC) and hippocampus (HIPP)/superior parietal cortex (sPAR).

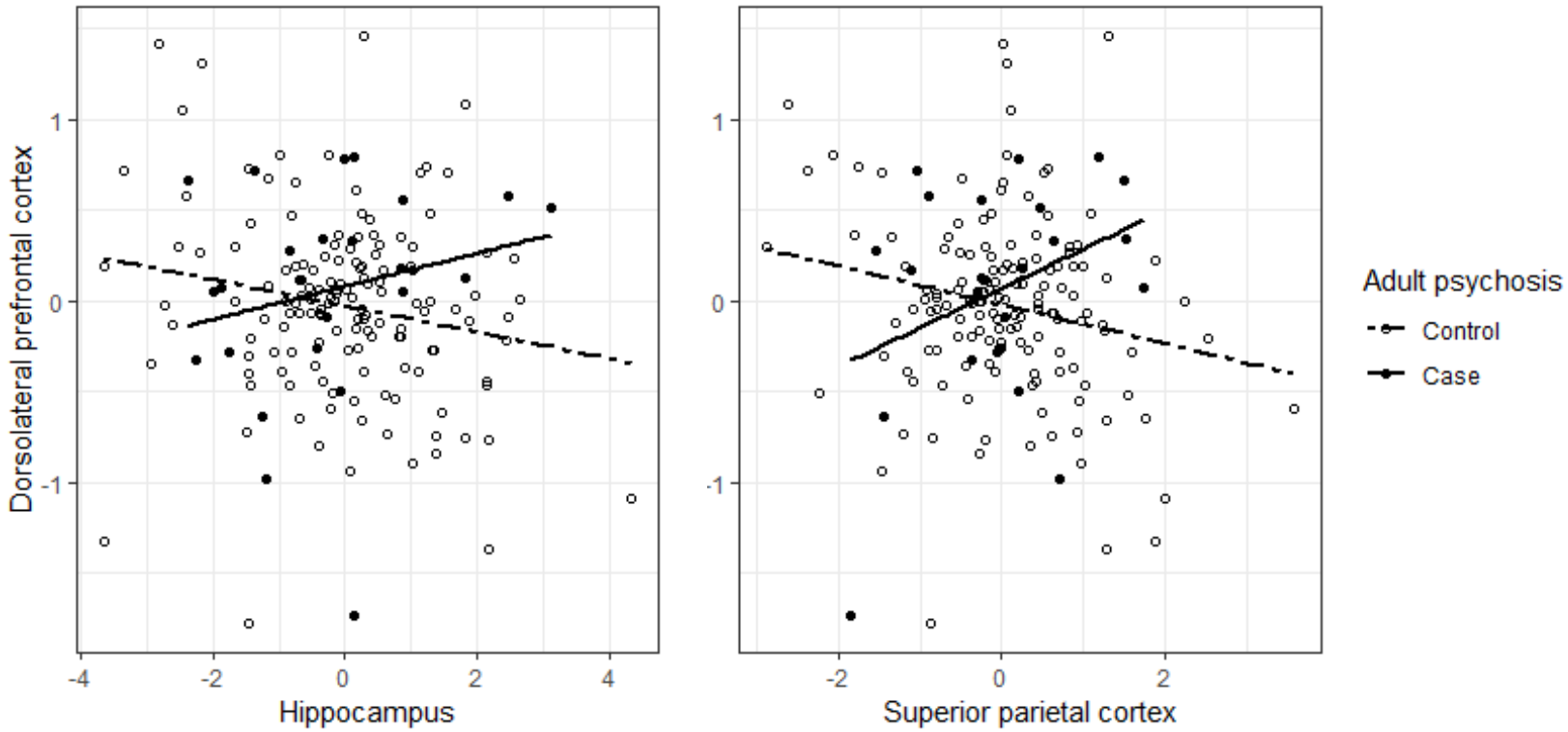
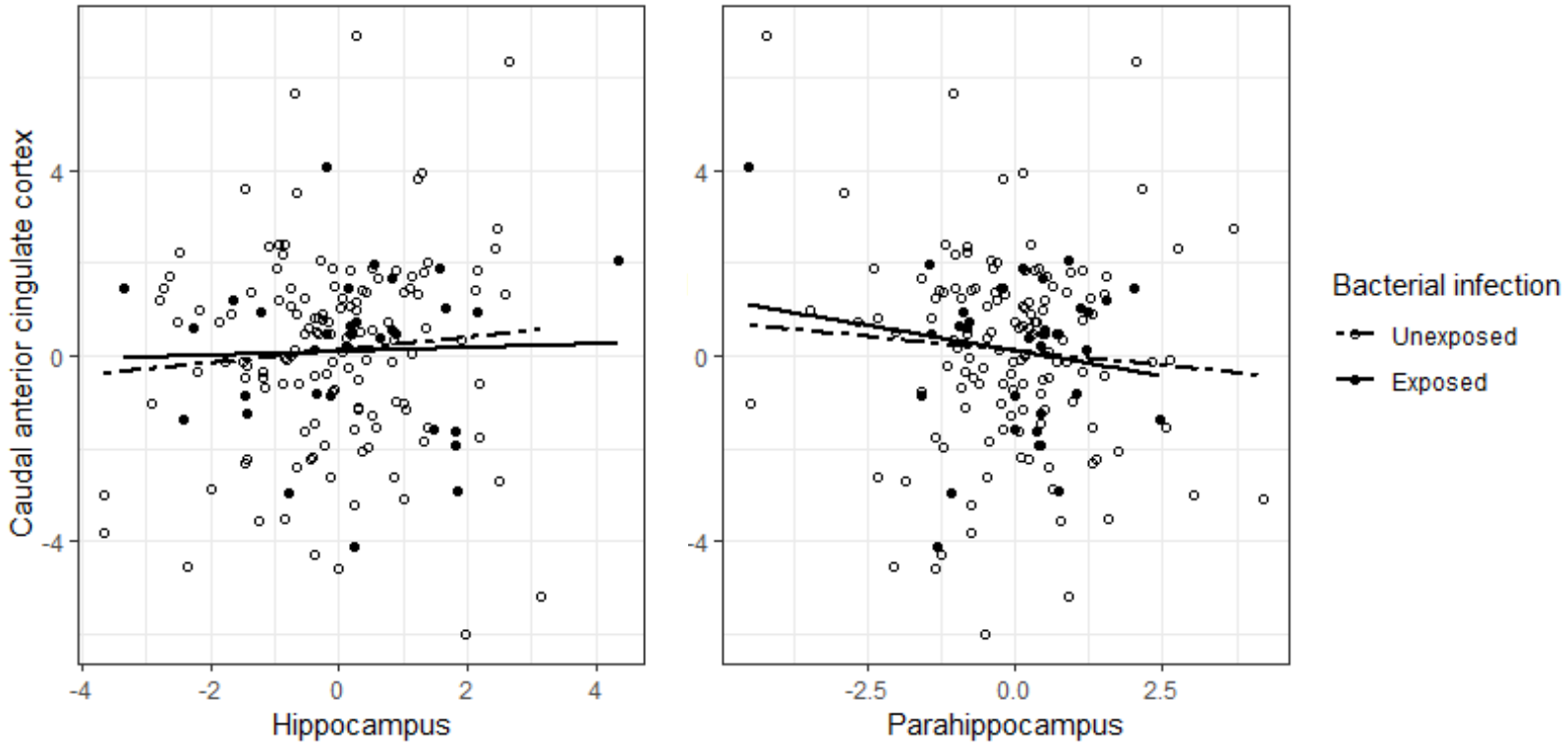


Figure 4.8.4 Associations between caudal anterior cingulate cortex (cACC) and hippocampus (HIPP)/parahippocampus (paraHIPP).



4.9 Supplementary Tables

Table 4.9.1 Box's M and Jennrich's tests for overall differences in covariance and correlation matrices by adult psychosis and prenatal bacterial infection.

	Box's M		*Jennrich*	
	χ^2	*p*	χ^2	*p*
Adult psychosis				
Average	30.90	0.08	33.74	0.00
Left hemisphere	24.70	0.26	22.76	0.09
Right hemisphere	39.46	0.01	38.70	0.00
Prenatal bacterial infection				
Average	31.70	0.06	22.24	0.10
Left hemisphere	40.09	0.01	19.84	0.18
Right hemisphere	29.11	0.11	27.30	0.03

Table 4.9.2 Comparison of demographic characteristics by participation in the magnetic resonance imaging (MRI) studies of the New England Family Study (NEFS) participants with psychoses (n=116).

		Participation in the MRI study		
		Participant	***Non-participant***	***p***
Sample size		26 (22.4)	90 (77.6)	
Categorical variables, n (%)				
Sex	Female	11 (42.3)	53 (58.9)	.91
	Male	15 (57.7)	37 (41.1)	
Maternal race/ethnicity	Non-white	5 (19.2)	22 (24.4)	.58
	White	21 (80.8)	68 (75.6)	
Study site	Boston	17 (65.4)	61 (67.8)	.82
	Providence	9 (34.6)	29 (32.2)	
Season of birth	Summer-Fall	21 (80.8)	68 (75.6)	.58
	Winter-Spring	5 (19.2)	22 (24.4)	
Continuous variables, mean (sd)				
Birth year		1962.62	1962.28	.45
Maternal education		11.19 (2.2)	10.5 (2.0)	.15
Parental socioeconomic status		5.4 (2.3)	5.4 (1.9)	.99
Any prenatal bacterial infection	Exposed	7 (26.9)	36 (40.0)	.22
	Unexposed	19 (73.1)	54 (60.0)	

Table 4.9.3 Descriptive statistics for hippocampal and parahippocampal volumes (divided by total intracranial volume).

		Hippocampus (mean ± sd)			Parahippocampus (mean ± sd)		
		Left	**Right**	**Average**	**Left**	**Right**	**Average**
All		.0180 ± .0023	.0185 ± .0020	.0091 ± .0010	.0099 ± .0013	.0093 ± .0011	.0048 ± .0005
Male	Psychotic	.0173 ± .0022	.0181 ± .0017	.0089 ± .0009	.0098 ± .0013	.0090 ± .0010	.0047 ± .0005
	Control	.0188 ± .0029	.0193 ± .0026	.0095 ± .0013	.0095 ± .0012	.0096 ± .0011	.0048 ± .0004
Female	Psychotic	.0184 ± .0021	.0187 ± .0019	.0100 ± .0013	.0100 ± .0013	.0094 ± .0010	.0049 ± .0005
	Control	.0172 ± .0024	.0176 ± .0026	.0098 ± .0013	.0098 ± .0013	.0091 ± .0013	.0047 ± .0006
Prenatal bacterial infection	Exposed	.0181 ± .0031	.0188 ± .0022	.0092 ± .0012	.0100 ± .0014	.0093 ± .0010	.0048 ± .0004
	Unexposed	.0179 ± .0021	.0184 ± .0019	.0091 ± .0010	.0099 ± .0013	.0093 ± .0011	.0048 ± .0005

Table 4.9.4 Pearson correlation coefficients between right hemisphere volumes of regions of interests (ROIs) among psychotic cases and controls.

	Adult psychosis		
	Case	***Control***	***Test statistic***
Pearson correlation and 95% bias-corrected and accelerated (BCa) bootstrap confidence interval			
HIPP-paraHIPP	.19 (-.23, .57)	.11 (-.05, .25)	Z = .38, p=.70
HIPP-sPAR	-.11 (-.47, .27)	-.11 (-.24, .03)	Z = .02, p=.98
HIPP-iPAR	**.57 (.25, .77)**	**.04 (-.14, .20)**	**Z = 2.70, p=.01**
HIPP-cACC	.27 (-.19, .64)	.01 (-.18, .17)	Z = 1.19, p=.23
HIPP-DLPFC	.26 (-.26, .64)	.03 (-.14, .19)	Z = 1.03, p=.30
paraHIPP-iPAR	**-.69 (-.86, -.44)**	**-.05 (-.21, .09)**	**Z = 3.55, p=.00**
paraHIPP-sPAR	.01 (-.37, .49)	-.02 (-.17, .15)	Z = .16, p=.87
paraHIPP-cACC	-.14 (-.44, .10)	-.08 (-.25, .09)	Z = .26, p=.79
paraHIPP-DLPFC	.09 (-.50, .55)	-.19 (-.35, -.03)	Z = 1.26, p=.21
sPAR-iPAR	-.18 (-.50, .23)	-.08 (-.24, .09)	Z = .44, p=.66
sPAR-cACC	.24 (-.16, .57)	-.14 (-.27, .01)	Z = 1.69, p=.09
sPAR-DLPFC	-.17 (-.63, .38)	-.08 (-.26, .13)	Z = .41, p=.68
iPAR-cACC	.27 (.00, .57)	-.11 (-.27, .09)	Z = 1.73, p=.08
iPAR-DLPFC	.07 (-.51, .56)	-.09 (-.23, .05)	Z = .71, p=.48
cACC-DLPFC	-.07 (-.35, .30)	.01 (-.13, .15)	Z = .35, p=.73

Abbreviations: HIPP, hippocampus; paraHIPP, parahippocampus; sPAR, superior parietal cortex; iPAR, inferior parietal cortex; cACC, caudal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex.

Table 4.9.5 Pearson correlation coefficients between right hemisphere volumes of regions of interests (ROIs) among exposed and unexposed individuals.

	Prenatal bacterial infection		
	Exposed	***Unexposed***	***Test statistic***
Pearson correlation and 95% bias-corrected and accelerated (BCa) bootstrap confidence interval			
HIPP-paraHIPP	.09 (-.32, .41)	.04 (-.12, .19)	Z = .26, p=.80
HIPP-sPAR	.05 (-.36, .52)	-.14 (-.28, .01)	Z = .91, p=.36
HIPP-iPAR	.17 (-.38, .55)	-.01 (-.20, .19)	Z = .87, p=.38
HIPP-cACC	-.26 (-.58, .08)	.00 (-.17, .17)	Z = 1.32, p=.19
HIPP-DLPFC	-.05 (-.40, .34)	.05 (-.16, .20)	Z = .50, p=.62
paraHIPP-iPAR	.22 (-.12, .56)	-.07 (-.26, .09)	Z = 1.44, p=.15
paraHIPP-sPAR	**.41 (.05, .67)**	**-.09 (-.22, .04)**	**Z = 2.54, p=.01**
paraHIPP-cACC	.02 (-.37, .44)	-.09 (-.28, .09)	Z = .52, p=.60
paraHIPP-DLPFC	**-.76 (-.86, -.57)**	**-.16 (-.33, .03)**	**Z = 4.04, p=.00**
sPAR-iPAR	.04 (-.23, .35)	-.08 (-.23, .08)	Z = .56, p=.57
sPAR-cACC	-.06 (-.36, .26)	-.07 (-.21, .07)	Z = .05, p=.96
sPAR-DLPFC	-.22 (-.52, .22)	-.19 (-.36, -.01)	Z = .11, p=.91
iPAR-cACC	-.08 (-.30, .24)	-.15 (-.28, .00)	Z = .32, p=.75
iPAR-DLPFC	-.34 (-.60, .05)	-.06 (-.19, .08)	Z = 1.42, p=.15
cACC-DLPFC	-.03 (-.45, .31)	.03 (-.12, .17)	Z = .29, p=.77

Abbreviations: HIPP, hippocampus; paraHIPP, parahippocampus; sPAR, superior parietal cortex; iPAR, inferior parietal cortex; cACC, caudal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex

4.10 Supplementary Figures

Figure 4.10.1 Associations between inferior parietal cortex (iPAR) and hippocampus (HIPP)/parahippocampus (paraHIPP).

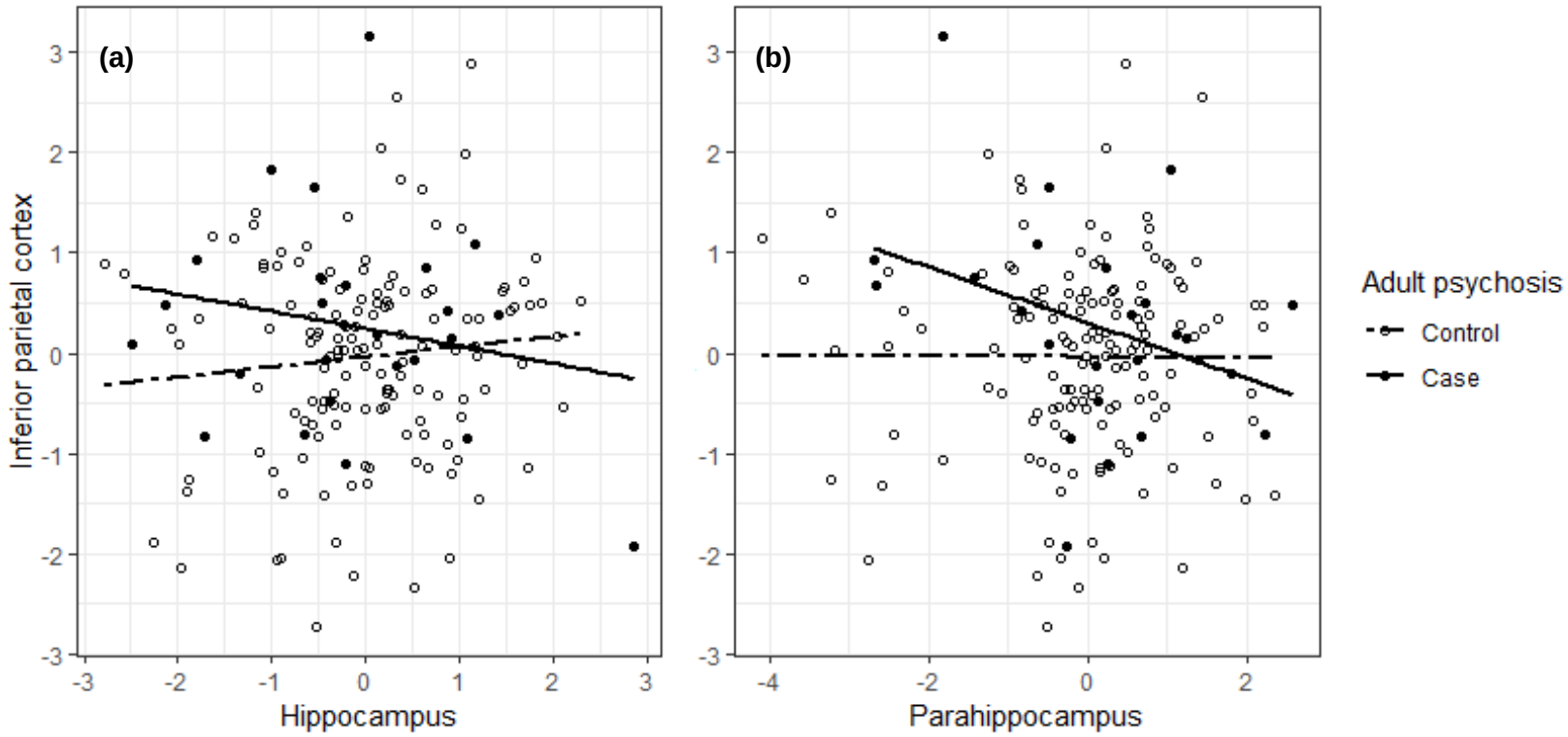
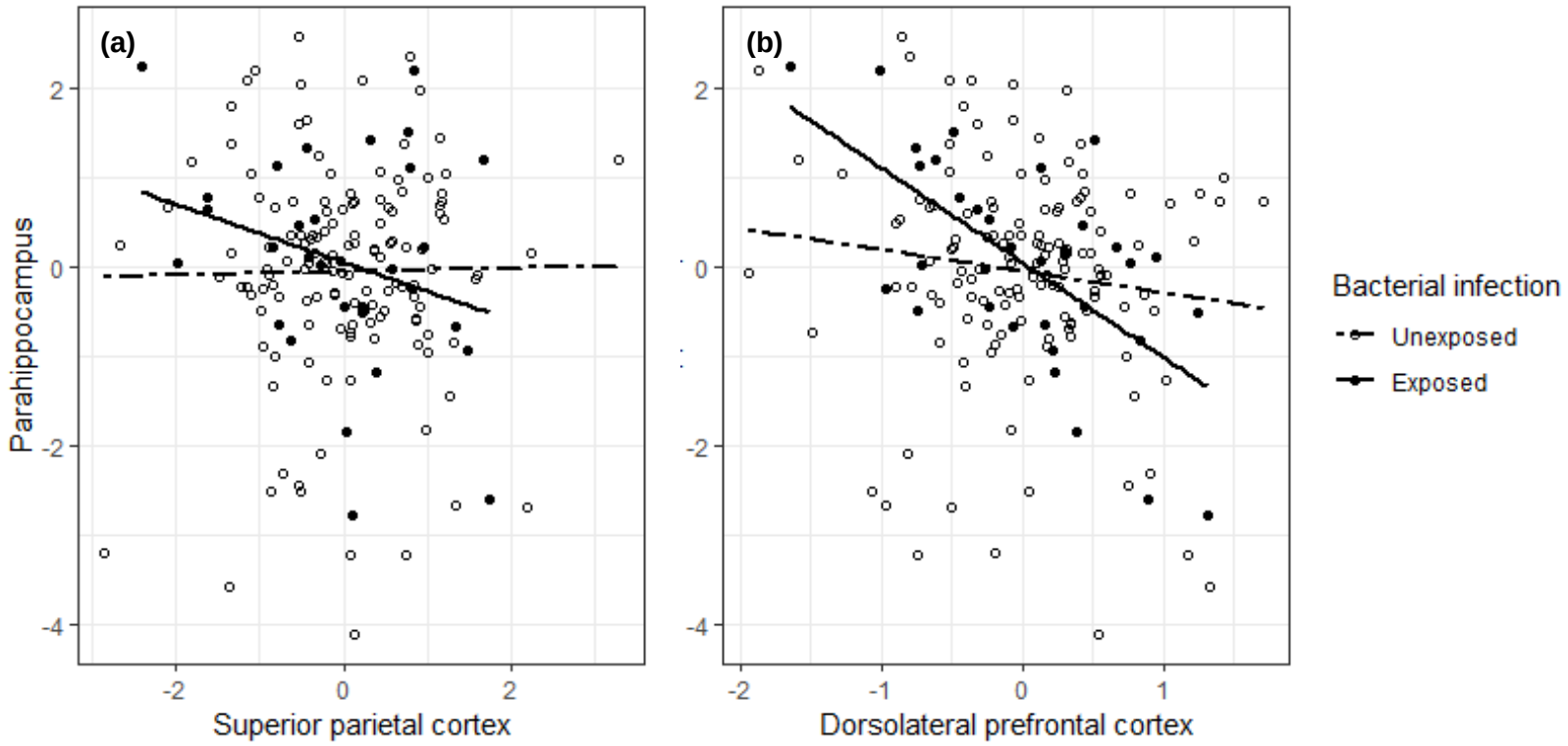


Figure 4.10.2 Associations between parahippocampus (paraHIPP) and superior parietal cortex (sPAR)/dorsolateral prefrontal cortex (DLPFC).



Appendix

Chapter 2: Acknowledgements to the New England Family Study

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Chapter 4: Acknowledgements the New England Family Study

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Bibliography

1. Perala J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsa E, Pirkola S, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry. 2007/01/03. 2007;64(1):19–28.

2. Tsai J, Rosenheck RA. Psychiatric comorbidity among adults with schizophrenia: A latent class analysis. Psychiatry Res [Internet]. 2013 Nov 30 [cited 2019 Mar 27];210(1):16–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23726869

3. Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature Mortality Among Adults With Schizophrenia in the United States. JAMA Psychiatry [Internet]. 2015 Dec 1 [cited 2019 Mar 27];72(12):1172. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26509694

4. Desai PR, Lawson KA, Barner JC, Rascati KL. Estimating the direct and indirect costs for community-dwelling patients with schizophrenia. J Pharm Heal Serv Res [Internet]. 2013 Dec 1 [cited 2019 Mar 27];4(4):187–94. Available from: http://doi.wiley.com/10.1111/jphs.12027

5. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Vol. 5. 2013.

6. Fatemi SH, Folsom TD. The Neurodevelopmental Hypothesis of Schizophrenia, Revisited. Schizophr Bull [Internet]. 2009;35(3):528–48. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2669580/

7. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? Br Med J (Clin Res Ed) [Internet]. 1987 Sep 19 [cited 2019 Mar 27];295(6600):681–2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3117295

8. Cannon M, Caspi A, Moffitt TE, Harrington H, Taylor A, Murray RM, et al. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. Arch Gen Psychiatry [Internet]. 2002 May [cited 2019 Mar 27];59(5):449–56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11982449

9. Fuller R, Nopoulos P, Arndt S, O'Leary D, Ho B-C, Andreasen NC. Longitudinal Assessment of Premorbid Cognitive Functioning in Patients With Schizophrenia Through Examination of Standardized Scholastic Test Performance. Am J Psychiatry [Internet]. 2002 Jul [cited 2019 Mar 27];159(7):1183–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12091197

10. Jones PB, Rantakallio P, Hartikainen AL, Isohanni M, Sipila P. Schizophrenia as a long-term outcome of pregnancy, delivery, and perinatal complications: a 28-year follow-up of

the 1966 north Finland general population birth cohort. Am J Psychiatry. 1998/03/21. 1998;155(3):355–64.

11. Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am J Psychiatry [Internet]. 2010;167(3):261–80. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20123911

12. Mikhail MS, Anyaegbunam A. Lower urinary tract dysfunction in pregnancy: a review. Obstet Gynecol Surv. 1995;50(9):675–83.

13. Mazor-Dray E, Levy A, Schlaeffer F, Sheiner E. Maternal urinary tract infection: is it independently associated with adverse pregnancy outcome? J Matern Fetal Neonatal Med [Internet]. 2008/12/17. 2009 Jan 7 [cited 2018 Nov 5];22(2):124–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19085630

14. Farkash E, Weintraub AY, Sergienko R, Wiznitzer A, Zlotnik A, Sheiner E. Acute antepartum pyelonephritis in pregnancy: a critical analysis of risk factors and outcomes. Eur J Obstet Gynecol Reprod Biol [Internet]. 2012 May [cited 2018 Nov 5];162(1):24–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22381037

15. McDermott S, Callaghan W, Szwejbka L, Mann H, Daguise V. Urinary tract infections during pregnancy and mental retardation and developmental delay. Obs Gynecol [Internet]. 2000;96(1):113–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10862853

16. Camp BW, Broman SH, Nichols PL, Leff M. Maternal and neonatal risk factors for mental retardation: defining the ‘at-risk’ child. Early Hum Dev [Internet]. 1998 Jan 9 [cited 2018 Aug 24];50(2):159–73. Available from: https://www.sciencedirect.com/science/article/pii/S0378373297000349?via%3Dihub

17. Caviness VS, Meyer J, Makris N, Kennedy DN. MRI-Based Topographic Parcellation of Human Neocortex: An Anatomically Specified Method with Estimate of Reliability. J Cogn Neurosci [Internet]. 1996 Nov 20 [cited 2019 Mar 24];8(6):566–87. Available from: http://www.mitpressjournals.org/doi/10.1162/jocn.1996.8.6.566

18. Kennedy DN, Lange N, Makris N, Bates J, Meyer J, Caviness VS. Gyri of the human neocortex: an MRI-based analysis of volume and variance. Cereb Cortex [Internet]. 1998 Jun [cited 2019 Mar 24];8(4):372–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9651132

19. Allen JS, Damasio H, Grabowski TJ, Bruss J, Zhang W. Sexual dimorphism and asymmetries in the gray-white composition of the human cerebrum. Neuroimage [Internet]. 2003 Apr [cited 2019 Mar 24];18(4):880–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12725764

20. Chen CH, Panizzon MS, Eyler LT, Jernigan TL, Thompson W, Fennema-Notestine C, et

al. Genetic influences on cortical regionalization in the human brain. Neuron [Internet]. 2011/11/22. 2011;72(4):537–44. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22099457

21. Colibazzi T, Zhu H, Bansal R, Schultz RT, Wang Z, Peterson BS. Latent volumetric structure of the human brain: Exploratory factor analysis and structural equation modeling of gray matter volumes in healthy children and adults. Hum Brain Mapp [Internet]. 2008 Nov 1 [cited 2019 Mar 24];29(11):1302–12. Available from: http://doi.wiley.com/10.1002/hbm.20466

22. He Y, Chen Z, Evans A. Structural Insights into Aberrant Topological Patterns of Large-Scale Cortical Networks in Alzheimer's Disease. J Neurosci [Internet]. 2008 Apr 30 [cited 2019 Mar 24];28(18):4756–66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18448652

23. Lerch JP, Worsley K, Shaw WP, Greenstein DK, Lenroot RK, Giedd J, et al. Mapping anatomical correlations across cerebral cortex (MACACC) using cortical thickness from MRI. Neuroimage [Internet]. 2006 Jul 1 [cited 2019 Mar 24];31(3):993–1003. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16624590

24. Mechelli A, Friston KJ, Frackowiak RS, Price CJ. Journal of Neuroscience. J Neurosci [Internet]. 2005 Sep 7 [cited 2019 Mar 24];23(27):9240–5. Available from: http://www.jneurosci.org/content/25/36/8303

25. Mitelman SA, Buchsbaum MS, Brickman AM, Shihabuddin L. Cortical intercorrelations of frontal area volumes in schizophrenia. Neuroimage [Internet]. 2005 Oct 1 [cited 2018 Dec 28];27(4):753–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15990338

26. Mitelman SA, Shihabuddin L, Brickman AM, Buchsbaum MS. Cortical intercorrelations of temporal area volumes in schizophrenia. Schizophr Res [Internet]. 2005 Jul 15 [cited 2018 Dec 28];76(2–3):207–29. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15949654

27. Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative Diseases Target Large-Scale Human Brain Networks. Neuron [Internet]. 2009 Apr 16 [cited 2019 Mar 24];62(1):42–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19376066

28. Abbs B, Liang L, Makris N, Tsuang MT, Seidman LJ, Goldstein JM. Covariance modeling of MRI brain volumes in memory circuitry in schizophrenia: Sex differences are critical. Neuroimage [Internet]. 2011 Jun 15 [cited 2018 Nov 1];56(4):1865–74. Available from: https://www.sciencedirect.com/science/article/pii/S1053811911003739?via%3Dihub

29. Seitz J, Kubicki M, Jacobs EG, Cherkerzian S, Weiss BK, Papadimitriou G, et al. Impact of sex and reproductive status on memory circuitry structure and function in early midlife using structural covariance analysis. Hum Brain Mapp [Internet]. 2019 Mar 12 [cited 2019

Mar 25];40(4):1221–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30548738

30. Sorensen HJ, Mortensen EL, Reinisch JM, Mednick SA. Association between prenatal exposure to bacterial infection and risk of schizophrenia. Schizophr Bull [Internet]. 2009;35(3):631–7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18832344

31. Babulas V, Factor-Litvak P, Goetz R, Schaefer CA, Brown AS. Prenatal exposure to maternal genital and reproductive infections and adult schizophrenia. Am J Psychiatry [Internet]. 2006;163(5):927–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16648337

32. Brown AS, Schaefer CA, Wyatt RJ, Goetz R, Begg MD, Gorman JM, et al. Maternal exposure to respiratory infections and adult schizophrenia spectrum disorders: a prospective birth cohort study. Schizophr Bull [Internet]. 2000;26(2):287–95. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10885631

33. Clarke MC, Tanskanen A, Huttunen MO, Whittaker JC, Cannon M. Evidence for an interaction between familial liability and prenatal exposure to infection in the causation of schizophrenia. Am J Psychiatry [Internet]. 2009;166(9):1025–30. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19487391

34. Goldstein JM, Buka SL, Seidman LJ, Tsuang MT. Specificity of familial transmission of schizophrenia psychosis spectrum and affective psychoses in the New England family study's high-risk design. Arch Gen Psychiatry [Internet]. 2010/05/05. 2010;67(5):458–67. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20439827

35. Goldstein JM, Cherkerzian S, Seidman LJ, Donatelli JA, Remington AG, Tsuang MT, et al. Prenatal maternal immune disruption and sex-dependent risk for psychoses. Psychol Med [Internet]. 2014/07/30. 2014;44(15):3249–61. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25065485

36. Meyer U, Feldon J. Epidemiology-driven neurodevelopmental animal models of schizophrenia. Prog Neurobiol [Internet]. 2010;90(3):285–326. Available from: http://www.sciencedirect.com/science/article/pii/S0301008209001695

37. Boksa P. Effects of prenatal infection on brain development and behavior: A review of findings from animal models. Brain Behav Immun [Internet]. 2010;24(6):881–97. Available from: http://www.sciencedirect.com/science/article/pii/S0889159110000589

38. Humann J, Mann B, Gao G, Moresco P, Ramahi J, Loh LN, et al. Bacterial Peptidoglycan Transverses the Placenta to Induce Fetal Neuroproliferation and Aberrant Postnatal Behavior. Cell Host Microbe [Internet]. 2016;19(3):388–99. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26962947

39. McCarthy MM. Sex differences in neuroimmunity as an inherent risk factor. Neuropsychopharmacology [Internet]. 2018; Available from:

https://doi.org/10.1038/s41386-018-0138-1

40. Goldstein JM, Seidman LJ, O'Brien LM, Horton NJ, Kennedy DN, Makris N, et al. Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. Arch Gen Psychiatry [Internet]. 2002/02/13. 2002;59(2):154–64. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11825137

41. Goldstein JM, Walder DJ. Sex differences in schizophrenia: the case for developmental origins. . In: Sharma T, Harvey PJ, editors. The Early Course of Schizophrenia . New York, NY: Oxford University Press; 2006. p. 143–73.

42. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a Complex Trait. Arch Gen Psychiatry [Internet]. 2003 Dec 1 [cited 2019 Feb 14];60(12):1187. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14662550

43. Dean K, Stevens H, Mortensen PB, Murray RM, Walsh E, Pedersen CB. Full spectrum of psychiatric outcomes among offspring with parental history of mental disorder. Arch Gen Psychiatry [Internet]. 2010;67(8):822–9. Available from: http://dx.doi.org/10.1001/archgenpsychiatry.2010.86

44. Van Os J, Rutten BPF, Poulton R. Gene-Environment Interactions in Schizophrenia: Review of Epidemiological Findings and Future Directions. Schizophr Bull [Internet]. 2008 Nov 1;34(6):1066–82. Available from: http://dx.doi.org/10.1093/schbul/sbn117

45. Niswander KR, Gordon M. The women and their pregnancies: The collaborative perinatal study of the National Institute of Neurological Diseases and Stroke. . Washington, DC: U. S. Government Printing Office; 1972.

46. Goldstein JM, Seidman LJ, Buka SL, Horton NJ, Donatelli JA, Rieder RO, et al. Impact of genetic vulnerability and hypoxia on overall intelligence by age 7 in offspring at high risk for schizophrenia compared with affective psychoses. Schizophr Bull [Internet]. 2000/07/08. 2000;26(2):323–34. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10885634

47. Seidman LJ, Buka SL, Goldstein JM, Horton NJ, Rieder RO, Tsuang MT. The relationship of prenatal and perinatal complications to cognitive functioning at age 7 in the New England Cohorts of the National Collaborative Perinatal Project. Schizophr Bull [Internet]. 2000/07/08. 2000 [cited 2018 Oct 25];26(2):309–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10885633

48. Seidman LJ, Giuliano AJ, Smith CW, Stone WS, Glatt SJ, Meyer EC, et al. Neuropsychological functioning in adolescents and young adults at genetic risk for schizophrenia and affective psychoses: results from the Harvard and Hillside Adolescent High Risk Studies. Schizophr Bull [Internet]. 2006/05/19. 2006;32(3):507–24. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16707777

49. Seidman LJ, Buka SL, Goldstein JM, Tsuang MT. Intellectual decline in schizophrenia: evidence from a prospective birth cohort 28 year follow-up study. J Clin Exp Neuropsychol [Internet]. 2006/02/18. 2006;28(2):225–42. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16484095

50. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders--Patient Edition, Version 2. Washington, DC: American Psychiatric Press; 1996.

51. Association AP. Diagnostic and statistical manual of mental disorders (DSM-IV). Am Psychiatry Assoc Washington, DC. 1994;

52. Myrianthopoulos NC, French KS. An application of the U.S. Bureau of the Census socioeconomic index to a large, diversified patient population. Soc Sci Med [Internet]. 1968 Sep 1 [cited 2018 Aug 24];2(3):283–99. Available from: https://www.sciencedirect.com/science/article/pii/0037785668900048

53. Krause D, Matz J, Weidinger E, Wagner J, Wildenauer A, Obermeier M, et al. The association of infectious agents and schizophrenia. World J Biol Psychiatry. 2010;11(5):739–43.

54. Goldstein JM, Cherkerzian S, Seidman LJ, Petryshen TL, Fitzmaurice GM, Tsuang MT, et al. Sex-specific rates of transmission of psychosis in the New England high-risk family study. Schizophr Res [Internet]. 2011/02/22. 2011;128(1–3):150–5. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21334180

55. SAS. 9.4. Cary, NC: SAS Institute; 2013.

56. Urakubo A, Jarskog LF, Lieberman JA, Gilmore JH. Prenatal exposure to maternal infection alters cytokine expression in the placenta, amniotic fluid, and fetal brain. Schizophr Res. 2001/02/13. 2001;47(1):27–36.

57. Brown AS, Hooton J, Schaefer CA, Zhang H, Petkova E, Babulas V, et al. Elevated maternal interleukin-8 levels and risk of schizophrenia in adult offspring. Am J Psychiatry. 2004;161(5):889–95.

58. Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Wagner RL, Yolken RH. Maternal cytokine levels during pregnancy and adult psychosis. Brain Behav Immun [Internet]. 2001;15(4):411–20. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11782107

59. Nielsen PR, Laursen TM, Mortensen PB. Association between parental hospital-treated infection and the risk of schizophrenia in adolescence and early adulthood. Schizophr Bull. 2011;39(1):230–7.

60. Goldstein JM, Cherkerzian S, Tsuang MT, Petryshen TL. Sex differences in the genetic risk for schizophrenia: history of the evidence for sex-specific and sex-dependent effects.

Am J Med Genet B Neuropsychiatr Genet [Internet]. 2013;162B(7):698–710. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24132902

61. Abel KM, Drake R, Goldstein JM. Sex differences in schizophrenia. Int Rev Psychiatry. 2010/11/05. 2010;22(5):417–28.

62. Ochoa S, Usall J, Cobo J, Labad X, Kulkarni J. Gender Differences in Schizophrenia and First-Episode Psychosis: A Comprehensive Literature Review. Schizophr Res Treatment [Internet]. 2012;2012:1–9. Available from: http://www.hindawi.com/journals/schizort/2012/916198/

63. Rosenfeld CS. Sex-Specific Placental Responses in Fetal Development. Endocrinology. 2015/08/05. 2015;156(10):3422–34.

64. Cvitic S, Longtine MS, Hackl H, Wagner K, Nelson MD, Desoye G, et al. The Human Placental Sexome Differs between Trophoblast Epithelium and Villous Vessel Endothelium. PLoS One [Internet]. 2013;8(10):e79233. Available from: https://doi.org/10.1371/journal.pone.0079233

65. Enninga EA, Nevala WK, Creedon DJ, Markovic SN, Holtan SG. Fetal sex-based differences in maternal hormones, angiogenic factors, and immune mediators during pregnancy and the postpartum period. Am J Reprod Immunol. 2014/08/06. 2015;73(3):251–62.

66. Kim-Fine S, Regnault TRH, Lee JS, Gimbel SA, Greenspoon JA, Fairbairn J, et al. Male gender promotes an increased inflammatory response to lipopolysaccharide in umbilical vein blood. J Matern Neonatal Med. 2012;25(11):2470–4.

67. Seidman LJ, Cherkerzian S, Goldstein JM, Agnew-Blais JC, Tsuang MT, Buka SL. Neuropsychological performance and family history in children at age 7 who develop adult schizophrenia or bipolar psychosis in the New England Family Studies. Psychol Med [Internet]. 2012/05/12. 2013;43(1):119–31. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22575089

68. Köhler O, Petersen L, Mors O, Mortensen PB, Yolken RH, Gasse C, et al. Infections and exposure to anti-infective agents and the risk of severe mental disorders: a nationwide study. Acta Psychiatr Scand. 2017;135(2):97–105.

69. Hung GCL, Pietras SA, Carliner H, Martin L, Seidman LJ, Buka SL, et al. Cognitive ability in childhood and the chronicity and suicidality of depression. Br J Psychiatry [Internet]. 2015/11/21. 2016;208(2):120–7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26585100

70. Gilman SE, Hornig M, Ghassabian A, Hahn J, Cherkerzian S, Albert PS, et al. Socioeconomic disadvantage, gestational immune activity, and neurodevelopment in early childhood. Proc Natl Acad Sci [Internet]. 2017 Jun 12 [cited 2018 Dec

3];114(26):201617698. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28607066

71. Köhler-Forsberg O, Petersen L, Gasse C, Mortensen PB, Dalsgaard S, Yolken RH, et al. A Nationwide Study in Denmark of the Association Between Treated Infections and the Subsequent Risk of Treated Mental Disorders in Children and AdolescentsA Nationwide Study of Infections and the Subsequent Risk of Mental Disorders in Children and Adolesc. JAMA Psychiatry [Internet]. 2019 Mar 1;76(3):271–9. Available from: https://doi.org/10.1001/jamapsychiatry.2018.3428

72. Khandaker GM, Zimbron J, Lewis G, Jones PB. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. Psychol Med [Internet]. 2013 Feb 16 [cited 2018 Oct 25];43(02):239–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22717193

73. Brown AS, Cohen P, Harkavy-Friedman J, Babulas V, Malaspina D, Gorman JM, et al. Prenatal rubella, premorbid abnormalities, and adult schizophrenia. Biol Psychiatry [Internet]. 2001 Mar 15 [cited 2018 Nov 10];49(6):473–86. Available from: http://linkinghub.elsevier.com/retrieve/pii/S000632230101068X

74. Ellman LM, Yolken RH, Buka SL, Torrey EF, Cannon TD. Cognitive Functioning Prior to the Onset of Psychosis: The Role of Fetal Exposure to Serologically Determined Influenza Infection. Biol Psychiatry [Internet]. 2009 Jun 15 [cited 2018 Nov 10];65(12):1040–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19195645

75. Emiru T, Beyene G, Tsegaye W, Melaku S. Associated risk factors of urinary tract infection among pregnant women at Felege Hiwot Referral Hospital, Bahir Dar, North West Ethiopia. BMC Res Notes [Internet]. 2013 Jul 25 [cited 2018 Nov 14];6:292. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23885968

76. Trabert B, Misra DP. Risk factors for bacterial vaginosis during pregnancy among African American women. Am J Obstet Gynecol [Internet]. 2007 Nov [cited 2018 Nov 14];197(5):477.e1-8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17980180

77. Howe LD, Tilling K, Galobardes B, Lawlor DA. Loss to follow-up in cohort studies: bias in estimates of socioeconomic inequalities. Epidemiology [Internet]. 2013 Jan [cited 2018 Nov 14];24(1):1–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23211345

78. Cochran WG, Rubin DB. Controlling Bias in Observational Studies: A Review. Sankhyā Indian J Stat Ser A [Internet]. 1973;35(4):417–46. Available from: http://www.jstor.org/stable/25049893

79. Greenland S, Robins JM. Identifiability, exchangeability, and epidemiological confounding. Int J Epidemiol [Internet]. 1986 Sep [cited 2018 Nov 14];15(3):413–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3771081

80. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research.

Epidemiology [Internet]. 1999 Jan [cited 2018 Nov 14];10(1):37–48. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9888278

81. Lee Y, Cherkerzian S, Seidman LJ, Papandonatos GD, Savitz DA, Tsuang MT, et al. Maternal bacterial infection during pregnancy and offspring's risk of psychoses: variation by severity of infection and offspring sex. Am J Psychiatry.

82. McDermott S, Mann JR, Wu J. Maternal Genitourinary Infection Appears to Synergistically Increase the Risk of Epilepsy in Children of Women with Epilepsy. Neuroepidemiology [Internet]. 2010;34(2):117–22. Available from: http://www.karger.com/DOI/10.1159/000268824

83. Seidman LJ, Goldstein JM, Goodman JM, Koren D, Turner WM, Faraone S V., et al. Sex differences in olfactory identification and Wisconsin Card Sorting performance in schizophrenia: relationship to attention and verbal ability. Biol Psychiatry [Internet]. 1997/07/15. 1997 Jul 15 [cited 2018 Nov 6];42(2):104–15. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9209727

84. Goldstein JM, Seidman LJ, Goodman JM, Koren D, Lee H, Weintraub S, et al. Are there sex differences in neuropsychological functions among patients with schizophrenia? Am J Psychiatry [Internet]. 1998/10/10. 1998 Oct [cited 2018 Nov 6];155(10):1358–64. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9766767

85. Mendrek A, Mancini-Marïe A. Sex/gender differences in the brain and cognition in schizophrenia. Neurosci Biobehav Rev [Internet]. 2016 Aug [cited 2018 Nov 6];67:57–78. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26743859

86. Meyer U, Nyffeler M, Engler A, Urwyler A, Schedlowski M, Knuesel I, et al. The Time of Prenatal Immune Challenge Determines the Specificity of Inflammation-Mediated Brain and Behavioral Pathology. J Neurosci [Internet]. 2006 May 3 [cited 2018 Oct 25];26(18):4752–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16672647

87. Sullivan R, Wilson DA, Feldon J, Yee BK, Meyer U, Richter-Levin G, et al. The international society for developmental psychobiology annual meeting symposium: Impact of early life experiences on brain and behavioral development. Dev Psychobiol [Internet]. 2006 Nov [cited 2018 Nov 6];48(7):583–602. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17016842

88. Entrican G. Immune regulation during pregnancy and host-pathogen interactions in infectious abortion. J Comp Pathol [Internet]. [cited 2019 Mar 27];126(2–3):79–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11944996

89. Sargent IL. Maternal and fetal immune responses during pregnancy. Exp Clin Immunogenet [Internet]. 1993 [cited 2019 Mar 27];10(2):85–102. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8251183

90. Broman S. The collaborative perinatal project: an overview. Handb Longitud Res. 1984;1:185–227.

91. Agnew-Blais JC, Buka SL, Fitzmaurice GM, Smoller JW, Goldstein JM, Seidman LJ. Early Childhood IQ Trajectories in Individuals Later Developing Schizophrenia and Affective Psychoses in the New England Family Studies. Schizophr Bull [Internet]. 2015/04/24. 2015;41(4):817–23. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25904723

92. Agnew-Blais JC, Seidman LJ, Fitzmaurice GM, Smoller JW, Goldstein JM, Buka SL. The interplay of childhood behavior problems and IQ in the development of later schizophrenia and affective psychoses. Schizophr Res [Internet]. 2017/01/08. 2017;184:45–51. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28062262

93. Stuart EA, Marcus SM, Horvitz-Lennon M V., Gibbons RD, Normand S-LT, Brown CH. Using Non-Experimental Data to Estimate Treatment Effects. Psychiatr Ann. 2009;

94. Rubin DB. The design versus the analysis of observational studies for causal effects: Parallels with the design of randomized trials. Stat Med [Internet]. 2007 Jan 15 [cited 2018 Nov 17];26(1):20–36. Available from: http://doi.wiley.com/10.1002/sim.2739

95. Mccaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat Med. 2013;

96. Imbens GW. Nonparametric estimation of average treatment effects under exogeneity: A review. In: Review of Economics and Statistics. 2004.

97. Ridgeway G. gbm: Generalized Boosted Regression Models. R Packag version 16-31. 2010;

98. McCaffrey DF, Ridgeway G, Morral A. Propensity score estimation with boosted regression for evaluating causal effects in observational studies. Psychol Methods. 2004;

99. Robins JM, Hernán M a, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology [Internet]. 2000 Sep [cited 2018 Nov 14];11(5):550–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10955408

100. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. Epidemiology. 2004;

101. Robins JM, Rotnitzky A, Zhao LP. Analysis of semiparametric regression models for repeated outcomes in the presence of missing data. J Am Stat Assoc. 1995;

102. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models [Internet]. Vol. 168, American Journal of Epidemiology. 2008 [cited 2018 Nov

16]. p. 656–64. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2732954/pdf/kwn164.pdf

103. Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. Psychol Methods. 2010;

104. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med [Internet]. 2015 Dec 10 [cited 2018 Dec 5];34(28):3661–79. Available from: http://doi.wiley.com/10.1002/sim.6607

105. Ho DE, Imai K, King G, Stuart EA. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. Polit Anal. 2007;

106. Stuart EA. Matching methods for causal inference: A review and a look forward. Stat Sci [Internet]. 2010 Feb 1 [cited 2018 Nov 16];25(1):1–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20871802

107. Rubin DB. Using Propensity Scores to Help Design Observational Studies: Application to the Tobacco Litigation. Heal Serv Outcomes Res Methodol [Internet]. 2001 [cited 2018 Nov 17];2(3/4):169–88. Available from: http://link.springer.com/10.1023/A:1020363010465

108. Lumley T. Analysis of Complex Survey Samples. J Stat Softw. 2004;

109. Carlsson A, Waters N, Carlsson ML. Neurotransmitter interactions in schizophrenia--therapeutic implications. Biol Psychiatry [Internet]. 1999 Nov 15 [cited 2018 Nov 10];46(10):1388–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10578453

110. Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R. Increased dopamine transmission in schizophrenia: relationship to illness phases. Biol Psychiatry [Internet]. 1999 Jul 1 [cited 2018 Nov 6];46(1):56–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10394474

111. Gilmore JH, Jarskog LF, Vadlamudi S, Lauder JM. Prenatal Infection and Risk for Schizophrenia: IL-1 [beta], IL-6, and TNF [alpha] Inhibit Cortical Neuron Dendrite Development. Neuropsychopharmacology. 2004;29(7):1221.

112. Innocenti GM, Price DJ. Exuberance in the development of cortical networks. Nat Rev Neurosci [Internet]. 2005 Dec 1 [cited 2018 Nov 30];6(12):955–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16288299

113. Mednick SA et al. Schizophrenia in High-Risk Children: Sex Differences in Predisposing Factors. [Internet]. 1977 [cited 2018 Nov 30]. Available from: https://eric.ed.gov/?id=ED145647

114. Aylward E, Walker E, Bettes B. Intelligence in Schizophrenia: Meta-analysis of the Research. Schizophr Bull [Internet]. 1984 Jan 1 [cited 2018 Nov 30];10(3):430–59. Available from: https://academic.oup.com/schizophreniabulletin/article-lookup/doi/10.1093/schbul/10.3.430

115. Goldstein JM, Seidman LJ, Santangelo S, Knapp PH, Tsuang MT. Are schizophrenic men at higher risk for developmental deficits than schizophrenic women? Implications for adult neuropsychological functions. J Psychiatr Res [Internet]. 1994/11/01. 1994;28(6):483–98. Available from: https://www.ncbi.nlm.nih.gov/pubmed/7699608

116. Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. Arch Gen Psychiatry [Internet]. 1998 May [cited 2019 Mar 24];55(5):433–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9596046

117. Wright IC, Rabe-Hesketh S, Woodruff PWR, David AS, Murray RM, Bullmore ET. Meta-Analysis of Regional Brain Volumes in Schizophrenia. Am J Psychiatry [Internet]. 2000 Jan 1 [cited 2019 Mar 24];157(1):16–25. Available from: http://psychiatryonline.org/doi/abs/10.1176/ajp.157.1.16

118. Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, et al. Abnormalities of the Left Temporal Lobe and Thought Disorder in Schizophrenia. N Engl J Med [Internet]. 1992 Aug 27 [cited 2018 Dec 28];327(9):604–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1640954

119. Job DE, Whalley HC, Johnstone EC, Lawrie SM. Grey matter changes over time in high risk subjects developing schizophrenia. Neuroimage [Internet]. 2005 May 1 [cited 2019 Mar 24];25(4):1023–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15850721

120. Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet (London, England) [Internet]. 2003 Jan 25 [cited 2019 Mar 24];361(9354):281–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12559861

121. Ellman LM, Deicken RF, Vinogradov S, Kremen WS, Poole JH, Kern D, et al. Structural brain alterations in schizophrenia following fetal exposure to the inflammatory cytokine interleukin-8. Schizophr Res [Internet]. 2010 Aug 1 [cited 2018 Nov 1];121(1–3):46–54. Available from: https://www.sciencedirect.com/science/article/pii/S0920996410013101?via%3Dihub

122. Alexander-Bloch A, Giedd JN, Bullmore E. Imaging structural co-variance between human brain regions. Nat Rev Neurosci [Internet]. 2013 May 27 [cited 2018 Dec 28];14(5):322–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23531697

123. Abbs B, Liang L, Makris N, Tsuang MT, Seidman LJ, Goldstein JM. Covariance

modeling of MRI brain volumes in memory circuitry in schizophrenia: Sex differences are critical. Neuroimage [Internet]. 2011/04/19. 2011;56(4):1865–74. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21497198

124. Box GEP. A general distribution theory for a class of likelihood criteria. Biometrika [Internet]. 1949 Dec [cited 2019 Mar 24];36(3–4):317–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15402070

125. Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, et al. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. Neuroimage [Internet]. 2010 Nov 15 [cited 2019 Mar 24];53(3):1135–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20006715

126. Jones PB, Harvey I, Lewis SW, Toone BK, Van Os J, Williams M, et al. Cerebral ventricle dimensions as risk factors for schizophrenia and affective psychosis: an epidemiological approach to analysis. Psychol Med [Internet]. 1994 Nov [cited 2019 Mar 24];24(4):995–1011. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7892367

127. Cannon TD, van Erp TGM, Rosso IM, Huttunen M, Lönnqvist J, Pirkola T, et al. Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. Arch Gen Psychiatry [Internet]. 2002 Jan [cited 2019 Mar 24];59(1):35–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11779280

128. Blokland GAM, del Re EC, Mesholam-Gately RI, Jovicich J, Trampush JW, Keshavan MS, et al. The Genetics of Endophenotypes of Neurofunction to Understand Schizophrenia (GENUS) consortium: A collaborative cognitive and neuroimaging genetics project. Schizophr Res [Internet]. 2018 May 1 [cited 2018 Nov 1];195:306–17. Available from: https://www.sciencedirect.com/science/article/pii/S0920996417305868?via%3Dihub

129. Goldstein JM, Lancaster K, Longenecker JM, Abbs B, Holsen LM, Cherkerzian S, et al. Sex differences, hormones, and fMRI stress response circuitry deficits in psychoses. Psychiatry Res [Internet]. 2015/04/29. 2015;232(3):226–36. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25914141

130. Mareckova K, Holsen LM, Admon R, Whitfield-Gabrieli S, Seidman LJ, Buka SL, et al. Neural - hormonal responses to negative affective stimuli: Impact of dysphoric mood and sex. J Affect Disord [Internet]. 2017/07/09. 2017;222:88–97. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28688266

131. Thermenos HW, Goldstein JM, Buka SL, Poldrack RA, Koch JK, Tsuang MT, et al. The effect of working memory performance on functional MRI in schizophrenia. Schizophr Res [Internet]. 2005/02/22. 2005;74(2–3):179–94. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15721998

132. Thermenos HW, Seidman LJ, Breiter H, Goldstein JM, Goodman JM, Poldrack RA, et al.

Functional magnetic resonance imaging during auditory verbal working memory in nonpsychotic relatives of persons with schizophrenia: a pilot study. Biol Psychiatry [Internet]. 2004/03/17. 2004;55(5):490–500. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15023577

133. Cabeza R, Ciaramelli E, Olson IR, Moscovitch M. The parietal cortex and episodic memory: an attentional account. Nat Rev Neurosci [Internet]. 2008 Aug [cited 2019 Mar 24];9(8):613–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18641668

134. Cirillo MA, Seidman LJ. Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. Neuropsychol Rev [Internet]. 2003 Jun [cited 2019 Mar 24];13(2):43–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12887039

135. Skinner EI, Fernandes MA. Neural correlates of recollection and familiarity: A review of neuroimaging and patient data. Neuropsychologia [Internet]. 2007 Jan 1 [cited 2019 Mar 24];45(10):2163–79. Available from: https://www.sciencedirect.com/science/article/pii/S0028393207001066

136. Squire LR, Stark CEL, Clark RE. THE MEDIAL TEMPORAL LOBE. Annu Rev Neurosci [Internet]. 2004 Jul 21 [cited 2019 Mar 24];27(1):279–306. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15217334

137. Stone WS, Faraone S V, Seidman LJ, Olson EA, Tsuang MT, Consortium on the Genetics on S. Searching for the liability to schizophrenia: concepts and methods underlying genetic high-risk studies of adolescents. J Child Adolesc Psychopharmacol [Internet]. 2005/08/12. 2005;15(3):403–17. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16092907

138. Thermenos HW, Seidman LJ, Poldrack RA, Peace NK, Koch JK, Faraone S V, et al. Elaborative verbal encoding and altered anterior parahippocampal activation in adolescents and young adults at genetic risk for schizophrenia using FMRI. Biol Psychiatry [Internet]. 2007/02/06. 2007;61(4):564–74. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17276751

139. Tulving E. Episodic Memory: From Mind to Brain. Annu Rev Psychol [Internet]. 2002 Feb [cited 2019 Mar 24];53(1):1–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11752477

140. Eichenbaum H. Hippocampus. Neuron [Internet]. 2004 Sep 30 [cited 2019 Mar 24];44(1):109–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15450164

141. Golby AJ, Poldrack RA, Brewer JB, Spencer D, Desmond JE, Aron AP, et al. Material-specific lateralization in the medial temporal lobe and prefrontal cortex during memory encoding. Brain [Internet]. 2001 Sep [cited 2019 Mar 24];124(Pt 9):1841–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11522586

142. Goldman-Rakic PS, Selemon LD, Schwartz ML. Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. Neuroscience [Internet]. 1984 Jul [cited 2019 Mar 24];12(3):719–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6472617

143. Krause BJ, Horwitz B, Taylor JG, Schmidt D, Mottaghy FM, Herzog H, et al. Network analysis in episodic encoding and retrieval of word-pair associates: a PET study. Eur J Neurosci [Internet]. 1999 Sep 1 [cited 2019 Mar 24];11(9):3293–301. Available from: http://doi.wiley.com/10.1046/j.1460-9568.1999.00723.x

144. Mesulam M-M. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol [Internet]. 1990 Nov [cited 2019 Mar 24];28(5):597–613. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2260847

145. Moscovitch M. The hippocampus as a "stupid," domain-specific module: Implications for theories of recent and remote memory, and of imagination. Can J Exp Psychol Can Psychol expérimentale [Internet]. 2008 Mar [cited 2019 Mar 24];62(1):62–79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18473631

146. Petrides M, Alivisatos B, Meyer E, Evans AC. Functional activation of the human frontal cortex during the performance of verbal working memory tasks. Proc Natl Acad Sci U S A [Internet]. 1993 Feb 1 [cited 2019 Mar 24];90(3):878–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8430101

147. Schacter DL, Addis DR. The ghosts of past and future. Nature [Internet]. 2007 Jan 3 [cited 2019 Mar 24];445(7123):27–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17203045

148. Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. Am J Psychiatry [Internet]. 2008 Aug [cited 2019 Mar 24];165(8):1015–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18381902

149. Goldstein JM, Goodman JM, Seidman LJ, Kennedy DN, Makris N, Lee H, et al. Cortical abnormalities in schizophrenia identified by structural magnetic resonance imaging. Arch Gen Psychiatry [Internet]. 1999/06/08. 1999;56(6):537–47. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10359468

150. Honea RA, Meyer-Lindenberg A, Hobbs KB, Pezawas L, Mattay VS, Egan MF, et al. Is gray matter volume an intermediate phenotype for schizophrenia? A voxel-based morphometry study of patients with schizophrenia and their healthy siblings. Biol Psychiatry [Internet]. 2008 Mar 1 [cited 2019 Mar 24];63(5):465–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17689500

151. Seidman LJ, Faraone S V, Goldstein JM, Kremen WS, Horton NJ, Makris N, et al. Left hippocampal volume as a vulnerability indicator for schizophrenia: a magnetic resonance

imaging morphometric study of nonpsychotic first-degree relatives. Arch Gen Psychiatry [Internet]. 2002/09/07. 2002;59(9):839–49. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12215084

152. Del Re EC, Gao Y, Eckbo R, Petryshen TL, Blokland GAM, Seidman LJ, et al. A New MRI Masking Technique Based on Multi-Atlas Brain Segmentation in Controls and Schizophrenia: A Rapid and Viable Alternative to Manual Masking. J Neuroimaging [Internet]. 2015/11/21. 2016;26(1):28–36. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26585545

153. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron [Internet]. 2002 Jan 31 [cited 2019 Mar 24];33(3):341–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11832223

154. Makris N, Meyer JW, Bates JF, Yeterian EH, Kennedy DN, Caviness VS. MRI-Based Topographic Parcellation of Human Cerebral White Matter and Nuclei. Neuroimage [Internet]. 1999 Jan [cited 2019 Mar 24];9(1):18–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9918726

155. da Silva AR, Malafaia G, Menezes IPP. biotools: an R function to predict spatial gene diversity via an individual-based approach. Genet Mol Res. 2017;16:gmr16029655.

156. Revelle W, Revelle MW. Package 'psych.' Compr R Arch Netw. 2015;

157. Canty A, Ripley B. Package 'boot.' 2017;

158. Davison AC, Hinkley D V. Bootstrap Methods and Their Application [Internet]. [cited 2019 Mar 25]. Available from: http://statwww.epfl.ch/davison/BMA/CUPsample.pdf

159. R: A language and environment for statistical computing [Internet]. Vienna, Austria; 2019. Available from: https://www.r-project.org/

160. Sullivan E V, Rosenbloom MJ, Desmond JE, Pfefferbaum A. Sex differences in corpus callosum size: relationship to age and intracranial size. Neurobiol Aging [Internet]. 2001;22(4):603–11. Available from: http://www.sciencedirect.com/science/article/pii/S0197458001002329

161. O'Brien LM, Ziegler DA, Deutsch CK, Kennedy DN, Goldstein JM, Seidman LJ, et al. Adjustment for whole brain and cranial size in volumetric brain studies: a review of common adjustment factors and statistical methods. Harv Rev Psychiatry [Internet]. 2006/06/22. 2006;14(3):141–51. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16787886

162. Mathalon DH, Sullivan E V., Rawles JM, Pfefferbaum A. Correction for head size in brain-imaging measurements. Psychiatry Res Neuroimaging [Internet]. 1993 Jun 1 [cited

2019 Mar 28];50(2):121–39. Available from: https://www.sciencedirect.com/science/article/pii/092549279390016B

163. Goldman-Rakic PS. Topography of Cognition: Parallel Distributed Networks in Primate Association Cortex. Annu Rev Neurosci [Internet]. 1988 Mar 28 [cited 2019 Mar 24];11(1):137–56. Available from: http://www.annualreviews.org/doi/10.1146/annurev.ne.11.030188.001033

164. Seltzer B, Van Hoesen GW. A direct inferior parietal lobule projection to the presubiculum in the rhesus monkey. Brain Res [Internet]. 1979 Dec 21 [cited 2019 Mar 24];179(1):157–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/116714

165. Barbas H, Pandya DN. Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. J Comp Neurol [Internet]. 1989 Aug 15 [cited 2019 Mar 24];286(3):353–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2768563

166. Sesack SR, Deutch AY, Roth RH, Bunney BS. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: An anterograde tract-tracing study withPhaseolus vulgaris leucoagglutinin. J Comp Neurol [Internet]. 1989 Dec 8 [cited 2019 Mar 24];290(2):213–42. Available from: http://doi.wiley.com/10.1002/cne.902900205

167. Makris N, Schlerf JE, Hodge SM, Haselgrove C, Albaugh MD, Seidman LJ, et al. MRI-based surface-assisted parcellation of human cerebellar cortex: an anatomically specified method with estimate of reliability. Neuroimage [Internet]. 2005/04/27. 2005;25(4):1146–60. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15850732

168. Arnold SE, Trojanowski JQ. Recent advances in defining the neuropathology of schizophrenia. Acta Neuropathol [Internet]. 1996 Sep [cited 2019 Mar 24];92(3):217–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8870823

169. Harrison PJ, Eastwood SL. Neuropathological studies of synaptic connectivity in the hippocampal formation in schizophrenia. Hippocampus [Internet]. 2001 Oct [cited 2019 Mar 24];11(5):508–19. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11732704

170. Bogerts B, Ashtari M, Degreef G, Alvir JM, Bilder RM, Lieberman JA. Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. Psychiatry Res [Internet]. 1990 Apr [cited 2019 Mar 24];35(1):1–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2367608

171. Carter CS, Perlstein W, Ganguli R, Brar J, Mintun M, Cohen JD. Functional Hypofrontality and Working Memory Dysfunction in Schizophrenia. Am J Psychiatry [Internet]. 1998 Sep [cited 2019 Mar 24];155(9):1285–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9734557

172. Heckers S, Rauch S, Goff D, Savage C, Schacter D, Fischman A, et al. Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. Nat

Neurosci [Internet]. 1998 Aug [cited 2019 Mar 24];1(4):318–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10195166

173. Bertolino A, Saunders RC, Mattay VS, Bachevalier J, Frank JA, Weinberger DR. Altered development of prefrontal neurons in rhesus monkeys with neonatal mesial temporo-limbic lesions: a proton magnetic resonance spectroscopic imaging study. Cereb Cortex [Internet]. 1997 Dec [cited 2019 Mar 25];7(8):740–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9408038

174. Weinberger DR, Berman KF, Suddath R, Torrey EF. Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. Am J Psychiatry [Internet]. 1992 Jul [cited 2019 Mar 24];149(7):890–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1609867

175. Fletcher P. The missing link: a failure of fronto-hippocampal integration in schizophrenia. Nat Neurosci [Internet]. 1998 Aug [cited 2019 Mar 24];1(4):266–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10195156

176. Meyer-Lindenberg AS, Olsen RK, Kohn PD, Brown T, Egan MF, Weinberger DR, et al. Regionally Specific Disturbance of Dorsolateral Prefrontal–Hippocampal Functional Connectivity in Schizophrenia. Arch Gen Psychiatry [Internet]. 2005 Apr 1 [cited 2019 Mar 24];62(4):379. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15809405

177. Godsil BP, Kiss JP, Spedding M, Jay TM. The hippocampal–prefrontal pathway: The weak link in psychiatric disorders? Eur Neuropsychopharmacol [Internet]. 2013 Oct 1 [cited 2019 Mar 25];23(10):1165–81. Available from: https://www.sciencedirect.com/science/article/pii/S0924977X12003136

178. Esslinger C, Walter H, Kirsch P, Erk S, Schnell K, Arnold C, et al. Neural Mechanisms of a Genome-Wide Supported Psychosis Variant. Science (80-) [Internet]. 2009 May 1 [cited 2019 Mar 25];324(5927):605–605. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19407193

179. Rasetti R, Sambataro F, Chen Q, Callicott JH, Mattay VS, Weinberger DR. Altered Cortical Network Dynamics. Arch Gen Psychiatry [Internet]. 2011 Dec 1 [cited 2019 Mar 25];68(12):1207. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21810628

180. Mody M, Cao Y, Cui Z, Tay K-Y, Shyong A, Shimizu E, et al. Genome-wide gene expression profiles of the developing mouse hippocampus. Proc Natl Acad Sci [Internet]. 2001 Jul 17 [cited 2019 Mar 24];98(15):8862–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11438693

181. van Erp TGM, Saleh PA, Rosso IM, Huttunen M, Lönnqvist J, Pirkola T, et al. Contributions of Genetic Risk and Fetal Hypoxia to Hippocampal Volume in Patients With Schizophrenia or Schizoaffective Disorder, Their Unaffected Siblings, and Healthy

Unrelated Volunteers. Am J Psychiatry [Internet]. 2002 Sep [cited 2019 Mar 24];159(9):1514–20. Available from: http://psychiatryonline.org/doi/abs/10.1176/appi.ajp.159.9.1514

182. Conrad AJ, Scheibel AB. Schizophrenia and the hippocampus: the embryological hypothesis extended. Schizophr Bull [Internet]. 1987 [cited 2019 Mar 24];13(4):577–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3438707

183. Fatemi SH, Emamian ES, Kist D, Sidwell RW, Nakajima K, Akhter P, et al. Defective corticogenesis and reduction in Reelin immunoreactivity in cortex and hippocampus of prenatally infected neonatal mice. Mol Psychiatry [Internet]. 1999 Mar [cited 2019 Mar 24];4(2):145–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10208446

184. Vaid RR, Yee BK, Shalev U, Rawlins JN, Weiner I, Feldon J, et al. Neonatal nonhandling and in utero prenatal stress reduce the density of NADPH-diaphorase-reactive neurons in the fascia dentata and Ammon's horn of rats. J Neurosci [Internet]. 1997 Jul 15 [cited 2019 Mar 24];17(14):5599–609. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9204941

185. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry [Internet]. 1987 Jul [cited 2019 Mar 25];44(7):660–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3606332

186. Jakob H, Beckmann H. Prenatal developmental disturbances in the limbic allocortex in schizophrenics. J Neural Transm [Internet]. 1986 Sep [cited 2019 Mar 24];65(3–4):303–26. Available from: http://link.springer.com/10.1007/BF01249090

187. Juottonen K, Laakso MP, Insausti R, Lehtovirta M, Pitkänen A, Partanen K, et al. Volumes of the entorhinal and perirhinal cortices in Alzheimer's disease. Neurobiol Aging [Internet]. [cited 2019 Mar 24];19(1):15–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9562498

188. van Hoesen GW, Hyman BT, Damasio AR. Entorhinal cortex pathology in Alzheimer's disease. Hippocampus [Internet]. 1991 Jan 1 [cited 2019 Mar 24];1(1):1–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1669339

189. Davis KD, Taylor KS, Hutchison WD, Dostrovsky JO, McAndrews MP, Richter EO, et al. Human anterior cingulate cortex neurons encode cognitive and emotional demands. J Neurosci [Internet]. 2005 Sep 14 [cited 2019 Mar 25];25(37):8402–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16162922

190. Toro R, Leonard G, Lerner J V, Lerner RM, Perron M, Bruce Pike G, et al. Prenatal Exposure to Maternal Cigarette Smoking and the Adolescent Cerebral Cortex. Neuropsychopharmacology [Internet]. 2008 [cited 2019 Mar 25];33:1019–27. Available from: www.neuropsychopharmacology.org

191. Büchel C, Coull JT, Friston KJ. The predictive value of changes in effective connectivity for human learning. Science [Internet]. 1999 Mar 5 [cited 2019 Mar 28];283(5407):1538–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10066177

192. BORGWARDT S, MCGUIRE P, ASTON J, GSCHWANDTNER U, PFLUGER M, STIEGLITZ R, et al. Reductions in frontal, temporal and parietal volume associated with the onset of psychosis. Schizophr Res [Internet]. 2008 Dec [cited 2019 Mar 28];106(2–3):108–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18789654

193. Prasad KM, Eack SM, Goradia D, Pancholi KM, Keshavan MS, Yolken RH, et al. Progressive Gray Matter Loss and Changes in Cognitive Functioning Associated With Exposure to Herpes Simplex Virus 1 in Schizophrenia: A Longitudinal Study. Am J Psychiatry [Internet]. 2011 Aug [cited 2019 Mar 25];168(8):822–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21632649

194. Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? Clin Neurosci [Internet]. 1995 [cited 2019 Mar 24];3(2):89–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7583624

195. Gold JM, Weinberger DR. Cognitive deficits and the neurobiology of schizophrenia. Curr Opin Neurobiol [Internet]. 1995 Apr [cited 2019 Mar 24];5(2):225–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7620311

196. Stephan KE, Baldeweg T, Friston KJ. Synaptic Plasticity and Dysconnection in Schizophrenia. Biol Psychiatry [Internet]. 2006 May 15 [cited 2019 Mar 24];59(10):929–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16427028