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Prenatal Infection and Schizophrenia: A Review of Epidemiologic and Translational Studies

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Abstract

An emerging literature from epidemiologic, clinical, and preclinical investigations has provided evidence that gestational exposure to infection contributes to the etiology of schizophrenia. In recent years, these studies have moved from ecologic designs, which ascertain infection based on epidemics in populations, to investigations that have capitalized on reliable biomarkers in individual pregnancies. These studies have documented specific candidate infections that appear to be associated with an elevated risk of schizophrenia. Animal models of maternal immune activation inspired by this work have revealed intriguing findings indicating behavioral, neurochemical, and neurophysiologic abnormalities consistent with observations in schizophrenia. In parallel studies in humans and animals, investigators are working to uncover the cellular and molecular mechanisms by which in utero exposure to infection contributes to schizophrenia risk. In this review, the authors discuss and critically evaluate the epidemiologic literature on in utero exposure to infection and schizophrenia, summarize emerging animal models of maternal immune activation, and discuss putative unique and common mechanisms by which in utero exposure to infection alters neurodevelopment, potentially increasing susceptibility to schizophrenia. The promise of this work for facilitating the identification of susceptibility loci in genetic studies of schizophrenia is illustrated by examples of interaction between in utero exposure to infection and genetic variants. The authors then elaborate on possible implications of this work, including the use of preventive measures for reducing the incidence of schizophrenia. Finally, they discuss new approaches aimed at addressing current challenges in this area of research.

For nearly 100 years, infectious microbes dominated discourse on the causes of disease. Fueled by the biomedical revolution and consequent advances in several other disciplines of medical research, however, interest in microbial pathogens beyond their classical role in infectious diseases began gradually to wane. Rather, medical research on diseases other than those considered to be infectious in nature continued to favor genetic and non-microbial etiologies of human illness.

Yet, in recent years, a proliferation of studies on infection as a risk factor for schizophrenia has emerged. If schizophrenia is a neurodevelopmental disorder, a hypothesis that is supported by converging evidence from several disciplines of research, then infection is a likely candidate risk factor, given that microbial pathogens have long been known to cause congenital brain anomalies. Rubella, herpes simplex virus, cytomegalovirus, toxoplasmosis, and other infections are potent disrupters of fetal neurodevelopment leading to abnormalities of brain and behavior, including mental retardation, learning disabilities, and hypoplasia of several brain regions (1). Consequently, investigators began to examine whether in utero

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exposure to infection was related to risk of schizophrenia. In the following two sections, we review the major ecologic and birth cohort studies of prenatal exposure to infection and schizophrenia. These studies were identified through searches of the PubMed database; the literature review was conducted from November 2008 to March 2009. Search terms included combinations of the following: prenatal, in utero, prenatal or in utero infection, prenatal or in utero influenza, prenatal or in utero exposure, schizophrenia, psychotic disorders, psychosis, neurodevelopment, infection, influenza, etiology, epidemic, pandemic, cohort, birth cohort, epidemiology, and reproductive outcomes. The search covered titles and abstracts and was restricted to English-language publications. References from studies retrieved were reviewed to identify additional articles. Studies were not limited to any particular research design.

Epidemiologic Evidence: Studies Based on Ecologic Data

The earliest studies of prenatal infection and schizophrenia were derived from studies that used ecologic data, namely, influenza epidemics in populations, to define exposure status (2) (Table 1). Initial studies provided evidence consistent with an association between second-trimester exposure to influenza epidemics and schizophrenia; further investigations, however, some of which were larger and featured more complete case ascertainment, failed to replicate the association. While similarly designed studies of other infectious agents have suggested potential relationships with schizophrenia, the effects have been generally weak, and few replication attempts have been made (2) (Table 2).

These results led many to question whether prenatal exposure to influenza and other infections is a risk factor for schizophrenia. Unfortunately, inadequate consideration was given to significant limitations of this work, the most prominent of which was diagnostic misclassification of influenza. In nearly all studies of prenatal influenza and schizophrenia, the presence of the exposure was based solely on whether an individual was in gestation at the time of an influenza epidemic, with no confirmation of maternal influenza infection during pregnancy. Hence, discrepant findings between studies may have resulted from nondifferential misclassification of influenza exposure, which biases effect sizes toward the null. For example, by relying solely on dates of birth to define exposure to influenza, approximately 70% of individuals who were in gestation during the 1957 type A2 influenza epidemic but were unexposed would have been misclassified as having been exposed (31).

Epidemiologic Evidence: Birth Cohort Studies

Consequently, a new approach was necessary to substantiate a link between prenatal exposure to infection and schizophrenia. Rather than relying on reports of epidemics in populations, we and other groups sought to document infection by measuring biomarkers in individual pregnancies and to relate confirmed exposure to the development of schizophrenia among individuals followed up into the age of risk for the disorder. This objective was achieved by capitalizing on well-characterized birth cohorts in which archived biological specimens or clinical diagnoses of infection were obtained during pregnancy and early life, and schizophrenia among offspring was systematically diagnosed following longitudinal assessment of offspring. We focus below on the major serological studies of prenatal infection and schizophrenia; further details are provided in Table 3. Studies based on infections identified from prospective maternal examinations and obstetric records are summarized in Table 4.

Influenza

Serologically documented prenatal exposure to influenza was examined in relation to schizophrenia in the Prenatal Determinants of Schizophrenia study (48), which was based on the birth cohort of the Child Health and Development Study (CHDS). This population-based cohort was born from 1959 to 1967 in Alameda County, Calif., and followed up for schizophrenia and other schizophrenia spectrum disorders in adulthood (Table 3). This investigation had several advantages, including archived maternal serum specimens prospectively drawn during pregnancy and stored frozen in a central repository; mothers belonging to the same health plan, which facilitated identification and follow-up of offspring with schizophrenia; and diagnoses confirmed with structured research interviews and psychiatric record review. Additional methodologic strengths included continuous follow-up assessments of offspring for schizophrenia, which allowed for adjustment for nondifferential loss to follow-up, and comparison subjects who were representative of the source population from which the cases were derived, which diminished the potential for bias due to loss to follow-up.

In a nested case-control study based on this cohort (37), our group demonstrated a threefold elevation in risk of schizophrenia following influenza exposure during the first half of gestation. For first-trimester exposure, the risk of schizophrenia was increased sevenfold. No elevated risk of schizophrenia was observed for influenza exposure during the second half of gestation, which suggests that these effects were specific to the period from early to midgestation.

Toxoplasma gondii (T. gondii)

T. gondii is a ubiquitous intracellular parasite that has been associated with several congenital CNS anomalies and more subtle delayed neurologic sequelae (1, 49). In the CHDS cohort, the risk of schizophrenia among individuals who were exposed in utero to elevated maternal *T. gondii* immunoglobin G (IgG) antibody, based on assay of archived maternal sera, was more than twice that of comparison subjects (38) (Table 3). A similar finding was demonstrated in an independent sample from Denmark in which *T. gondii* IgG was assayed in filter paper blood spots collected from offspring with schizophrenia and comparison offspring within 1 week of birth (45). Since *T. gondii* IgG antibody in infant blood almost certainly derived from the maternal rather than the fetal immune response, the latter finding can be considered a replication.

Herpes Simplex Virus Type 2 (HSV-2)

HSV-2 is a sexually transmitted virus, and maternal-offspring transmission generally occurs during passage through the birth canal. Neonatal exposure to HSV-2 is associated with congenital anomalies similar to those of gestational exposure to *T. gondii*, including neuropsychiatric outcomes (50). Three studies (32, 34, 40) have specifically investigated the relationship between prenatal exposure to HSV-2 and risk of schizophrenia among offspring. Two of these studies were derived from selected sites of the Collaborative Perinatal Project (CPP), a multisite study of population-based birth cohorts born from 1959 to 1967 throughout the United States that featured a number of methodologic advantages over earlier studies. Similar to the CHDS, archived maternal samples were prospectively drawn throughout pregnancy and stored in a central repository. The CPP also included follow-up for psychotic disorders in offspring at psychiatric treatment facilities using specified protocols and confirmation of diagnoses by psychiatric interviews and medical record reviews.

In the first of these studies (32), in the Providence, R.I., cohort of the CPP, maternal IgG antibody levels to HSV-2 were associated with a significantly elevated risk of psychosis (both nonaffective and affective) in offspring. Offspring in the highest quartile and decile for maternal HSV-2 antibody levels had odds ratios of 3.4 and 4.4, respectively, for risk of schizophrenia. In a much larger follow-up study (34), which included 200 case subjects with psychotic disorders and more than 500 matched comparison subjects from three cohorts of the CPP (Boston, Providence, and Philadelphia), a statistically significant 1.6-fold elevation in risk of psychosis and a significant 1.8-fold elevation in risk of schizophrenic psychoses were observed among offspring of mothers who were seropositive for HSV-2. The elevated risk was confined to offspring of sero-positive mothers who did not regularly use contraception and had frequent intercourse.

In an investigation of prenatal HSV-2 exposure and schizophrenia based on the CHDS birth cohort that included 60 case subjects and 120 comparison subjects, these associations were not replicated (40), with odds ratios near 1 for all analyses. The discrepant results between the CPP study and the CHDS may be accounted for by several methodologic differences. First, the CPP cohort included a larger proportion of African Americans than the CHDS cohort. As noted by Buka et al. (34), the higher prevalence of HSV-2 in this ethnic group may have provided greater statistical power to detect an association in the overall sample. The number of cases of schizophrenic psychoses in the latter CPP study (N=108) was also significantly greater than that of the CHDS cohort (N=60), further increasing statistical power. Hence, the null results from the CHDS may have been due in part to lack of power to detect an association between prenatal HSV-2 exposure and schizophrenia.

The second difference is related to exposure status. In the two CPP studies, the definition of exposure in the primary analyses was based on differing criteria: the first study restricted the measure of exposure to maternal HSV-2 IgG antibody levels, while the reported data of the latter study were based on the presence of maternal seropositivity to HSV-2 (although it was noted that quantitative data from that study were consistent with the results based on seropositivity). In the study from the CHDS cohort, no associations were demonstrated regardless of whether the exposure was defined in terms of HSV-2 seropositivity or IgG antibody levels.

Third, loss to follow-up could not be quantified in the CPP because of lack of access to population denominators over the follow-up period. While significant loss to follow-up also occurred in the CHDS, bias was probably more likely to have been mitigated in that cohort by the use of survival analytic methods, which was made possible by continuous follow-up of the cohort.

Finally, the CHDS, unlike the CPP, did not have access to data on sexual risk behaviors. Conceivably, associations between HSV-2 and schizophrenia may have been demonstrated if this more vulnerable subgroup had been analyzed separately, as in the CPP study.

Cytokines

Cytokines are a family of soluble polypeptides that play an essential role in the immune response as the systemic mediators of the host response to infection. Hence, these molecules represent robust markers of infectious and inflammatory conditions (51). In an investigation based on the CHDS birth cohort (36), we observed a nearly twofold elevation in maternal levels of interleukin-8 (IL-8), a pro-inflammatory chemokine (chemokines are a subclass of the cytokine superfamily), during the second trimester and the early third trimester among pregnancies giving rise to offspring with schizophrenia, relative to matched comparison subjects (Table 3). In the sample from the Providence site of the CPP cohort, levels of tumor necrosis factor-α (TNF-α), a proinflammatory cytokine, at the time of birth were significantly increased among mothers of offspring with psychosis (nonaffective and affective psychoses combined) relative to comparison subjects (33).

Although the reasons for the discrepant findings between the two studies are not entirely clear, some potential explanations may be considered. First, in the CPP study, the mean maternal IL-8 level was not significantly elevated in pregnancies that gave rise to offspring with psychoses, but analyses that classified IL-8 as a categorical variable revealed a "significant and graded association" between maternal serum IL-8 levels and offspring adult psychosis (although the data corresponding to the latter finding were not reported) (32). With regard to other cytokines, the two studies were in agreement with regard to maternal inter-leukin-1β (IL-1β) and interleukin-6 (IL-6), neither of which was associated with schizophrenia or psychotic disorders, and maternal interleukin-2 (IL-2), which was examined only in the CPP study, was not associated with psychoses.

Causal Mechanisms: Unique Effects of Infections

Both epidemiologic and preclinical studies promise to shed light on causal mechanisms by which prenatal exposure to infection might lead to schizophrenia. One school of thought contends that individual infections act to influence risk of schizophrenia by unique effects. This hypothesis is supported by the fact that infections associated with schizophrenia differ significantly from one another in several respects, including duration, antigenicity and antibody response, capacity to traverse the placenta, gestational specificity on known congenital outcomes, and effects on brain development. The alternative hypothesis, reviewed in the next section, is that infections act via one or more common mechanisms to increase vulnerability to schizophrenia.

While a detailed review of the individual characteristics and pathogenic effects of each infection is beyond the scope of this article, we discuss, as one example, potential mechanisms by which toxoplasmosis might act to increase schizophrenia risk. Mechanisms relevant to active primary infection by *T. gondii* appear to be unlikely, given that maternal or neonatal seropositivity to *T. gondii* IgM-specific antibody, a robust indicator of recently acquired infection, was not observed in two studies of *T. gondii* and schizophrenia (38, 45). A second potential mechanism involves reactivation of a previous infection, resulting in an inflammatory response in the developing fetal brain. An increase in maternal IgG antibody can result from this anamnestic response. A third possible explanation for the finding is a dormant *T. gondii* infection, which may be accompanied by elevated *T. gondii* IgG antibody up to many years after the infection. Neuropathologic effects could potentially ensue from exposure to this antibody, which can cross the placenta. Intriguingly, elevated total IgG antibody has teratogenic effects in certain autoimmune disorders (52).

Preclinical Studies of Prenatal Exposure to Influenza

Preclinical approaches to infection with a specific microbe have thus far been restricted to inoculation of pregnant rodents with influenza, followed by behavioral, neurophysiologic, molecular, and neuroanatomic assessments (53, 54). In offspring from pregnancies in which intranasal infusion of influenza in midpregnancy was administered, decreased exploratory behavior, diminished contact with novel objects, reduced "social" behavior, and prepulse inhibition deficits to acoustic startle were observed (54). The prepulse inhibition deficit was reversed following treatment with clozapine and chlorpromazine. Neonatal exposure to influenza has been associated with significant reductions in reelin-positive Cajal-Retzius cells in several cortical layers and the hippocampus but without changes in calretinin and neuronal nitric oxide synthase, which suggests that the effect is not due solely to greater cell death but also to abnormal reelin production (53). Decreased cortical and hippocampal area and an increase in pyramidal cell density in cortex were also observed in neonatally infected mice.

Causal Mechanisms: Common Effects of Infection

In an alternative, more parsimonious model, infections are postulated to act through common pathways to alter fetal brain development and increase vulnerability to schizophrenia. Gilmore and Jarskog (55) proposed that one such common mechanism involves infection-induced cytokines, and this hypothesis has now been extensively tested in animal models based on the seminal findings of Patterson (56) and the work of other groups.

Clinical Evidence

While physiologic levels of cytokines play critical roles in normal brain development, elevations of these inflammatory mediators secondary to maternal infection increase vulnerability to developmental brain damage (57). Intra-uterine exposure to elevated levels of infection-induced cytokines has been associated with chorioamnionitis, periventricular leukomalacia, and cerebral palsy. These abnormalities may develop as a result of several potential mechanisms, including stimulation of microglia and astroglia to produce nitric oxide and excitatory amino acids and disrupted maturation of oligodendrocytes, potentially contributing to white matter abnormalities, which have been associated with schizophrenia (58).

Most infections are associated with increases in several cytokines, including IL-8 and TNF-α, both of which have been associated with schizophrenia and other psychotic disorders, as reviewed above. Maternal serum IL-8 levels are associated with histologic chorioamnionitis in term infants, and maternal and fetal levels of IL-8 have been significantly correlated with one another. IL-8 belongs to the chemokine family and appears to be especially important for neutrophil attraction as well as discharge of lysosomal enzymes from neutrophils, leading to oxygen free radicals. TNF-α has also been associated with chorioamnionitis (59), and increased amniotic fluid levels of this cytokine have been associated with fetal infection (60). Polymorphisms in TNF-α genes have also been associated with schizophrenia (61).

Preclinical Evidence: Studies of Maternal Immune Activation

The vast majority of preclinical studies of infection have implemented an experimental paradigm involving maternal immune activation, as reviewed by Patterson (56).

Two agents have been used to induce immune activation during pregnancy: polyinosinic:polycytidylic acid (poly I:C), a synthetic analogue of double-stranded RNA, which mimics a viral infection, and lipopolysaccharide, a bacterial cell wall endotoxin. Interestingly, several brain and behavioral deficits in offspring were similar regardless of whether they resulted from maternal influenza or poly I:C (54). Offspring exposed to maternal immune activation also displayed dopaminergic abnormalities, including elevated amphetamine-induced locomotion, increased striatal dopamine release, and disrupted latent inhibition, the last of which was reversed by clozapine, suggesting elevated sensitivity of subcortical and mesolimbic dopaminergic pathways. Maternal immune activation exposure also resulted in increased locomotion after administration of the *N*-methyl-D-aspartic acid antagonist MK-801, which is consistent with glutamatergic models of schizophrenia (62, 63). In several preclinical maternal immune activation models, the observed phenotypes were not demonstrated during the juvenile period but emerged when testing occurred during adulthood, possibly modeling the developmental time course of the onset of schizophrenia.

Accumulating evidence from preclinical studies suggests potential mechanisms by which elevated cytokines might contribute to the observed brain and behavioral abnormalities implicated in schizophrenia. For example, direct treatment of embryonic rat cortical cultures with IL-1β and TNF-α led to dose-dependent decreases in immunoreactivity for MAP-2 antibody (64), which suggests that cytokines decrease cerebral cortical neuronal survival during brain development.

Although both maternal and fetal cytokines are elevated after immune activation, few studies have tested for a direct causal connection between cytokines and brain and behavioral abnormalities. Recently, Smith et al. (65) provided intriguing evidence supporting an important role for IL-6 in these outcomes in an animal model. They found that a single maternal injection of IL-6 in midpregnancy resulted in prepulse inhibition and latent inhibition deficits in adult offspring. Most of these effects were prevented after administration of anti-IL-6 antibody and by an IL-6 genetic knockout. While these findings do not prove that IL-6 is the sole contributor to the schizophrenia-related phenotypes resulting from maternal immune activation, they suggest a key role for this cytokine in the pathogenic process.

Gene-Environment Interplay

It has been widely acknowledged that genes and environmental exposures probably act in tandem to increase the risk of neuropsychiatric disorders, including schizophrenia. A gene-infection interaction in schizophrenia would be tested by assessing whether the presence of a susceptibility gene increases the effect of a prenatal infectious exposure on the risk of this disorder. Although no previous study has tested for interactions between individual susceptibility genes and prenatal infections in schizophrenia, a recent investigation using data from a large Finnish cohort revealed that prenatal exposure to pyelonephritis was demonstrated to have a fivefold greater effect on risk of schizophrenia among individuals with a family history of psychosis compared to those with no family history (47).

Genetic Effects on Neurodevelopment

As reviewed in detail elsewhere, a considerable number of putative vulnerability genes for schizophrenia have been identified, and several of these associations have been replicated in multiple studies (66, 67). While many of these genes will not be directly involved in infectious or inflammatory processes, they may act in concert with prenatal infection to increase liability to schizophrenia by disrupting neurodevelopmental events. Intriguingly, evidence is emerging that two prominent putative susceptibility genes—DISC1 and neuregulin—appear to play critical roles in brain development (68–71). Polymorphisms of these two genes have been associated with schizophrenia in several populations throughout the world, and mutations in these genes have resulted in brain and behavioral anomalies similar to those observed in the maternal immune activation model.

Table 5 presents comparisons of specific brain and behavioral anomalies observed in studies of animal models of maternal immune activation, DISC1, and neuregulin. Animal model studies of DISC1 and neuregulin-1 were identified through searches of the PubMed database conducted from November 2008 to May 2009. Search terms were derived from the characterization of maternal immune activation as described in a recent comprehensive review by Patterson (56). To limit the scope of the material, only DISC1 and neuregulin-1 studies that described phenotypes that were similar or related to the maternal immune activation model as described in Patterson (56) were included in Table 5. Additional search strategies were employed as described at the start of this article.

Genetic Effects on the Immune Response

In a second example of gene-environment interaction, infection alters the effect of genes that are central to the immune response. A group of particularly strong candidate genes that may be involved in this process are those that encode major histocompatibility complex (MHC) class I proteins, which present antigens to T lymphocytes at the cell surface. These

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molecules are enriched at the synapse, are required for normal synaptic function and synaptic remodeling, and play a particularly important role in graded fine-tuning of plasticity; their expression is regulated by cytokines (88). Under this model, prenatal infection and the consequent cytokine response may act to modify MHC class I function to a greater degree among individuals who are genetically predisposed to decreased function of this class of molecules, resulting in reduced synaptic plasticity, which has been postulated to play an important role in the pathophysiology of schizophrenia (89). Interestingly, genetic variants in the extended MHC represented one of the few results to meet genome-wide significance in three recent large-scale genome-wide association studies (90–92).

Attributable Proportion and Gene Identification

A concept that is particularly salient to the interpretation of gene-environment interaction is that of attributable proportion, which is defined as the proportion of case subjects in the population who would not have developed the disease if a cause were removed (93). This is theoretically similar to the "causal pie" models elaborated by other authors (93, 94). One key implication of this notion is that in the presence of gene-environment interaction, it would be an oversimplification to conclude that individual environmental risk factors or susceptibility genes "explain" a particular proportion of cases in the population.

This concept has implications for facilitating gene identification. While recent molecular genetic studies promise to interrogate the genome with greater precision than has ever been realized, it appears doubtful, in our view, that a sole focus on gene-finding will lead to definitive causes if gene-environment interaction plays a significant role. If the effect of certain susceptibility genes on risk of schizophrenia is dependent on prenatal infection, then an alternative and potentially more productive approach to gene identification would be to scan the genome in a subset of the population that has been exposed to the infection in question.

Implications of Research on Prenatal Exposure to Infection and Schizophrenia

Implications for Prevention

Investigations of prenatal exposure to infection in schizophrenia may have implications for prevention of the disorder. In this regard, the concept of attributable proportion also offers the potential to estimate the relative importance of preventive efforts. Attributable proportion is dependent on the magnitude of the effect of a component cause, the prevalence of the component cause in the population studied, and the nature of the interaction between component causes (94). Given that influenza, *T. gondii*, and genital/reproductive infections are highly prevalent and associations between prenatal exposure to each of these pathogens and schizophrenia were observed in our previous studies, we calculated the attributable proportion corresponding to the individual and combined effects of these infections using the data acquired from these studies and the standard published formula (94). The results are presented in Table 6. Given that little overlap was observed between these infections in the schizophrenia case and comparison subjects of the CHDS cohort (A.S. Brown et al., unpublished data), the attributable proportion for the combined effects of these infections is approximately the sum of the individual values. Hence, based on our data, we estimate that nearly one-third of schizophrenia cases could have been prevented if these infections had been entirely eliminated from the pregnant population. While it is unlikely that complete eradication of any infectious pathogen can be practically achieved, and although this finding clearly requires replication in an independent sample, this result raises the possibility that reducing the occurrence of prenatal exposure to influenza infection could nonetheless bring about an appreciable decline in the prevalence of schizophrenia.

Although estimates of attributable proportion have not been calculated for most putative risk factors for schizophrenia, the potential contribution of infection appears to be comparable to many of these other factors, based on similarities in effect sizes and population prevalence. For example, with regard to paternal age greater than 40, most groups have demonstrated effect sizes of at least twofold, and Malaspina et al. (95) calculated an attributable proportion of 26.6%. The effect sizes for low birth weight/prematurity and hypoxia, obstetric exposures that have been well replicated in studies of schizophrenia, are generally similar in magnitude to those demonstrated in studies of prenatal exposure to infection (96).

If gene-environment interaction contributes to the attributable proportion estimate for schizophrenia, as discussed in the preceding section, then “correcting” the genetic defects may not be necessary in order to eliminate subsets of schizophrenia cases that are accounted for by interactions between genetic and environmental factors. Rather, elimination of the environmental factor, such as prenatal infection, may be a more practical and feasible approach in many cases than one that targets the gene or its translated protein.

Recommendations for Public Health Practice

If associations between prenatal exposure to infection and schizophrenia are independently replicated in other cohorts, there may be cause for optimism given that many microbial infections are either treatable or preventable. Indeed, it is worth considering that the overall decline in bacterial illnesses and initiation of immunization programs may have reduced the incidence of schizophrenia since the 1950s, as suggested by Suvisaari et al. (97).

With regard to treatment, many genital/reproductive system microbes are readily eliminated by antibiotics. Hence, increased surveillance and treatment of the reproductive-age population for these infections may have the potential to reduce the risk of schizophrenia. This class of infections includes sexually transmitted diseases, such as HSV-2, which are preventable by barrier contraceptives.

The prevention of influenza has been a preoccupation of modern medicine for the past several decades. The elevated vulnerability of the mother and fetus to influenza has resulted in the inclusion of pregnant women as a group to be targeted for the vaccination. In our view, this strategy has potential benefits but possibly also certain risks. Routine administration of influenza vaccine during pregnancy will clearly mitigate the potential for exposure to influenza. Nonetheless, this benefit will need to be weighed against the expected exposure in the population of large numbers of pregnant women, most of whom would never have developed influenza, to an agent that may induce a cytokine response. This could have the undesired effect of inducing unnecessary damage to the developing fetal brain. These questions are particularly salient in light of the recent emergence of the H1N1 flu epidemic.

It has long been known that toxoplasmosis during pregnancy is preventable by relatively straightforward hygienic approaches, including avoidance of contamination from cat litter boxes and gardening and thorough cooking of meats, poultry, and fish to kill *T. gondii* oocysts. It is worth bearing in mind, however, that schizophrenia was shown to be related to elevated maternal *T. gondii* IgG levels (38, 45), not the presence of the parasite itself, which suggests that most infections were acquired before pregnancy. Since acquisition of *T. gondii* can occur throughout the life course, it may be worth considering measures to reduce exposure to this infection in the general population as early as childhood as well as to investigate measures of screening for, and reducing levels of, *T. gondii* IgG in women of reproductive age, especially those who are planning a pregnancy.

A New Proposed Research Agenda

Infectious Exposures and Molecular Genetic Studies

In our view, several strategies for research will be critical for advancing and refining the hypothesis that prenatal exposure to infection plays a role in the etiology of schizophrenia. First, we recommend the incorporation of prospectively documented, specific, and validly measured infectious exposures into molecular genetic studies of gene-environment interaction. While relatively few in number, approaches to identifying gene-environment interaction that have modeled genes in the same way as environmental exposures have yielded potentially groundbreaking findings (98, 99). Genome-wide association studies have generally yielded small effect sizes of individual genetic variants (100, 101). If the findings of existing gene-environment interaction studies represent a valid gauge of what we might expect from studies of susceptibility genes and prenatal infections, we anticipate that enriching the sample for the presence of these exposures will enhance the “signal” of susceptibility genes, particularly those that influence brain development or are involved in pathogenic mechanisms related to microbial etiologies. Other promising approaches to characterizing genetic influences, including the identification of copy number variants and epigenetic effects, should also be facilitated by research designs that document specific prenatal infections that have been demonstrated to interact with the genome and epigenome.

Translational Approaches

The adoption of translational approaches that capitalize on findings from epidemiologic research has considerable potential for integrating etiologic and pathophysiologic research in schizophrenia. As reviewed above, animal models have yielded evidence that prenatal exposure to infection causes phenotypes that appear to resemble brain and behavioral anomalies observed in schizophrenia. In our view, translational research aimed at leveraging this line of inquiry toward elucidating causal mechanisms by which neurodevelopment is altered by these prenatal insults should be given high priority. This will require interdisciplinary efforts between epidemiologists, geneticists, and molecular/cellular neuroscientists.

Windows of Vulnerability

In our opinion, greater attention needs to be devoted to understanding critical windows of vulnerability to infectious insults and the effects of these exposures on developmental trajectories. As exemplified by the epidemiologic studies reviewed above, the gestational timing of infection might be a critical factor influencing the risk of schizophrenia. Unfortunately, there has been a persistence of the notion that the effect of prenatal infection is isolated to midgestation. We contend that a more complicated scenario, in which the developmental window of vulnerability varies by type of infectious exposure, is more consistent with the empirical evidence and with our understanding of neurodevelopmental influences in general.

Conclusions

Epidemiologic studies have yielded evidence suggesting that prenatal exposure to infection plays a role in the etiology of schizophrenia. The use of biomarkers of prenatal infection in rigorous epidemiologic designs of birth cohorts followed into the age of risk for schizophrenia is a potentially useful new approach to either confirming or refuting findings from ecologic studies, identifying new microbial risk factors, and uncovering pathogenic mechanisms. In our view, research efforts aimed at discovering interactions between prenatal exposure to infection and susceptibility genes hold promise toward improving our understanding of both the genetic and the environmental bases of schizophrenia. The development of effective treatments for infectious diseases was one of the greatest successes of 20th-century medical science and was a major factor in the advent of modern medicine. The identification of microbial risk factors required rigorous and painstaking epidemiologic studies, and we expect that efforts in the 21st century to discover infectious causes of schizophrenia, as well as other diseases previously considered to be noninfectious, will be no less challenging. Nonetheless, given the high prevalence of microbial disease in pregnancy and ready access to existing treatments and preventive approaches to combat infectious illness, it is conceivable that these efforts will ultimately have an appreciable impact on the incidence and burden of schizophrenia in the global population.

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TABLE 1

Ecologic and Maternal Report Studies of Prenatal Exposure to Influenza and Development of Schizophrenia

					Comments[b]		
Authors, Year (Reference)	**Epidemic and Region**	**Numbers of Cases**	**Numbers of Noncases**	**Description of Association[a]**	**Strengths**	**Limitations**	**Other**
Mednick et al., 1988 (3)	1957 A2 epidemic in Uusimaa County, Finland	216 exposed cases, 1,565 unexposed cases	Not reported	2nd trimester	Exposed and unexposed cases matched by birth month	Data collected only to age 26	Data reported as proportion of cases with schizophrenia among all hospitalized cases with psychiatric disorders
Kendell and Kemp, 1989 (4)	1918–1919 and 1957 influenza A epidemics in Edinburgh, Scotland	Edinburgh Case Register: 122 exposed cases, 210 unexposed cases; Scottish national data: 227 exposed cases, 525 unexposed cases	Not reported	1957 epidemic in Edinburgh: 6th month; no associations for Scottish national data			Increased incidence of Parkinson's disease in those exposed to 1918–1919 pandemic
Barr et al., 1990 (5)	Epidemics between 1911 and 1950 in Denmark	7,239 cases; exposure status of individual cases not reported	Not reported	6th month	Large national sample; data adjusted for seasonality	Relatively low schizophrenia birthrate (2.4 per 1,000); this may be due to strict diagnostic criteria	
O'Callaghan et al., 1991 (6)	1957 A2 epidemic in England and Wales	339 exposed cases, 1,331 unexposed cases	Live births during exposure years: 126,959; average live births during unexposed years: 126,327; number of noncases not reported	5 months after peak of epidemic, births of individuals who developed schizophrenia were 88% higher than average in the corresponding previous and subsequent 2 years, females only		Several years of discharge records were missing from data	
Sham et al., 1992 (7)	Outbreaks from 1939 to 1960 in England and Wales	14,830 cases; exposure status of individual cases not reported	Not reported	3rd–7th month; 1.4% increase in number of schizophrenia births for every 1,000 deaths attributed to influenza			Examined temporal trends between influenza prevalence and schizophrenia births
Adams et al., 1993 (8)	Outbreaks from 1911 to 1960 in Scotland, England, and Denmark	Scotland: 16,960 cases (broad criteria), 8,229 cases (narrow criteria); England: 22,021 cases; Denmark: 18,723 cases (broad criteria), 14,260	Not reported	1957 A2 epidemic in Scotland and England: 4th month; England, general outbreaks: 6th–7th month; 1957 A2 epidemic in Denmark: 4th– 6th month; 1918–1919 pandemic in Denmark: no association;	Large national samples	Data sets were limited to cases still under psychiatric care after January 1963 (Scotland) or	Scottish and Danish cases were determined using both broad (any diagnosis of schizophrenia) and narrow (discharge diagnosis of schizophrenia on at least two occasions) diagnostic criteria

Authors, Year (Reference)	Epidemic and Region	Numbers of Cases	Numbers of Noncases	Description of Association[a]	Comments[b]: Strengths	Comments[b]: Limitations	Comments[b]: Other
		(narrow criteria); exposure status of individual cases not reported		associations were strongest in females		April 1969 (Denmark)	
Takei et al., 1993 (9)	Outbreaks from 1938 to 1965 in England and Wales	6,982 cases; exposure status of individual cases not reported	Not reported	5th month, females only			Inverse relationship between female schizophrenia births and affective psychosis births
Erlenmeyer-Kimling et al., 1994 (10)	1957 A2 influenza epidemic in Croatia	348 exposed cases, 3,761 unexposed cases	Live births during exposure period: 77,662; average live births during unexposed years: 81,559.5	None	National sample		
McGrath and Castle, 1995 (11)	Outbreaks in 1954, 1957, and 1959 in Queensland, Australia	1954 outbreak: 234 exposed cases, 1,985 unexposed cases; 1957 outbreak: 220 exposed cases, 1,938 unexposed cases; 1959 outbreak: 193 cases from index year, 1,921 cases from comparison year	33,688 exposed noncases, 336,475 unexposed noncases	4th month, 1954 epidemic, males only; 5th month, 1957 epidemic, females only; no association, 1959 epidemic			Southern Hemisphere study
Mednick et al., 1994 (12)	1957 A2 epidemic in Helsinki	25 cases total; 2nd trimester: 15 exposed cases, 13 with “definite influenza infection”; 1st and 3rd trimester: 10 exposed cases, 2 with “definite influenza infection”; no unexposed cases	Not reported	2nd trimester		Small number of cases; of 50 cases, only 25 had records; no unexposed group or comparison group	
Selten and Slaets, 1994 (13)	1957 A2 epidemic in the Netherlands	873 exposed cases, 3,761 unexposed cases	77,680 exposed noncases; average number of live births during unexposed years: 79,468	None	Large national sample		
Susser et al., 1994 (14)	1957 A2 influenza epidemic in the Netherlands	183 exposed cases, 808 unexposed cases	99,205 exposed noncases, 400,708 unexposed noncases	None	Large national sample		

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					Comments[b]		
Authors, Year (Reference)	Epidemic and Region	Numbers of Cases	Numbers of Noncases	Description of Association[a]	Strengths	Limitations	Other
Takei et al., 1994 (15)	Outbreaks from 1938 to 1965 in England and Wales	138 exposed cases; average of unexposed cases born during four comparison years: 148.5	Not reported	5 months after epidemics, females only (relative risk=1.07, 95% CI=1.02–1.13)			Poisson regression used to determine correlation between influenza prevalence and schizophrenia births; replication of 1993 study, but eliminated subjects born during 1958 Asian flu pandemic, responsible for significant effect in the previous study
Kunugi et al., 1995 (16)	1957 A/B mixed and A2 epidemic in Japan	133 exposed cases; average of unexposed cases per year during comparison years: 116.5	Not reported	5 months after A/B type epidemic, females only		Excluded patients who were in remission at time of the study	
Takei et al., 1995 (17)	Outbreaks from 1947 to 1969 (except the epidemic year 1958) in the Netherlands	"Typical" schizophrenia patients: 4,726 cases; "less typical": 5,389 cases; exposure status of individual cases not reported	Not reported	None			Poisson regression used to determine correlation between influenza prevalence and schizophrenia births; cases divided into typical schizophrenia patients (hebephrenic type, catatonic type, paranoid type, residual schizophrenia) and "less typical" schizophrenia (acute schizophrenic episode, latent schizophrenia, schizoaffective type, unspecified schizophrenia); trend was stronger in "typical" patients, but not significant
Takei et al., 1996 (18)	Outbreaks from 1915 to 1970 in Denmark	9,462 cases; exposure status of individual cases not reported	Not reported	6 months after outbreaks (relative risk=1.12, 95% CI=1.01– 1.2); population attributable risk fraction was 1.4%			First hospital admission series; Poisson regression used to determine correlation between influenza prevalence and schizophrenia births; findings stronger for narrow diagnostic criteria (schizophrenia, no affective psychosis) than for broad criteria (including affective psychosis)

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Authors, Year (Reference)	Epidemic and Region	Numbers of Cases	Numbers of Noncases	Description of Association[a]	Comments[b]: Strengths	Comments[b]: Limitations	Comments[b]: Other
Grech et al., 1997 (19)	Epidemics from 1923 to 1965 in England and Wales	Paranoid schizophrenia: 2,897 cases; non-paranoid schizophrenia: 14,350 cases; exposure status of individual cases not reported	Not reported	None			Data covered 80% of population; examined temporal trends between influenza prevalence and schizophrenia births; groups subdivided into paranoid schizophrenia and non-paranoid schizophrenia (other subtype of schizophrenia or diagnosis with-out reference to diagnostic subtype)
Morgan et al., 1997 (20)	Six epidemics from 1950 to 1960 in Australia	342 exposed cases, 134 unexposed cases	Exposed live births: 82,963; unexposed live births: 32,462	None	Exposed and unexposed matched by trimester; geographically well-defined population with low migration rate		1st-trimester exposure associated with increased risk of mental retardation
Selten et al., 1998 (21)	1957 A2 epidemic in Antillean and Surinamese immigrants in the Netherlands	57 Antillean cases and 16 Surinamese cases; exposure status of individual cases not reported	Live births, 1958: 522; live births, 1956: 489; live births, 1959: 454; exposure status not reported; no data from 1957, 1960	None			Increase in depression among exposed
Izumoto et al., 1999 (22)	1957 A2 influenza epidemic in Kochi, Japan	188 exposed cases, 22,754 unexposed cases	753 exposed noncases; 93,297 unexposed noncases	2nd trimester, females only (relative risk=2.86, 95% CI=1.37–5.26)	Included both inpatient and outpatient schizophrenia cases	Did not control for confounders	
Westergaard et al., 1999 (23)	Epidemics from 1950 to 1988 in Denmark	2,669 cases total; 6th month[c], influenza prevalence; “low”: 2,198 exposed cases; “intermediate”: 225 exposed cases; “high”: 246 exposed cases	Total size of cohort: 1,746,366	None			Birth order and influenza prevalence used as proxy measures for exposure to prenatal infection; prevalence categorized as low, intermediate, or high for influenza notifications of <5, 5–9, or ≥10 per 1,000 population, respectively; number of siblings and sibling interval used as proxy measures for exposure to childhood infections; large sibship (4 or more siblings) associated with increased risk of schizophrenia

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Authors, Year (Reference)	Epidemic and Region	Numbers of Cases	Numbers of Noncases	Description of Association[a]	Comments[b]		
					Strengths	Limitations	Other
Mino et al., 2000 (24)	1957–1958, 1962, and 1965 epidemics in Japan	1957: 165 exposed cases, 972 unexposed cases; 1962: 191 exposed cases, 653 unexposed cases; 1965: 150 exposed cases, 584 unexposed cases	Not reported	None		Subjects derived from many different randomly selected facilities in Japan; used place of residence in lieu of place of birth	
Limosin et al., 2003 (25)	Epidemics from 1949 to 1981 in France	974 cases total; 4th month: 49 exposed cases; 5th month: 57 exposed cases; 6th month: 45 exposed cases; 7th month: 37 exposed cases; number of unexposed cases not reported	974 noncases total; 4th month: 34 exposed noncases; 5th month: 36 exposed noncases; 6th month: 43 exposed noncases; 7th month: 44 exposed noncases; Number of unexposed noncases not reported	5th month (odds ratio=1.61, 95% CI=1.04–2.49) (case subjects compared to healthy unrelated comparison subjects); (odds ratio=2.24, 95% CI=1.49–3.35) (case subjects compared to siblings)	All subjects were interviewed to confirm diagnosis or comparison group status		Compared influenza prevalence and schizophrenia births; comparison subjects included nonschizophrenic siblings and matched nonsibling comparison subjects; some comparison subjects had DSM-IV diagnoses (anxiety, affective, substance-use, and personality disorders); mothers of case patients were slightly but significantly older than comparison subjects

[a]Measures of effect (relative risk, rate ratio, or odds ratio) are reported here if reported in the original paper; $p \leq 0.05$ unless otherwise noted. “Nth month” indicates gestational month of exposure. Rather than estimating gestational age, some studies reported the number of months after the peak of an epidemic during which schizophrenia births increased. This distinction is noted in the table.

[b]Many studies used similar designs. These columns include only notable departures from common features of the studies presented below. All of the studies in the Table share the following limitations (unless otherwise indicated): ecologic data and psychiatric registries to determine exposure and case status, respectively. Calculation of trimester of exposure assumed full-term pregnancy.

[c]Data reported here only for 6th month for this study; findings were similar for 4th and 5th months.

TABLE 2

Ecologic Studies of Prenatal Exposure to Infections Other Than Influenza and Development of Schizophrenia

					Comments[b]		
Authors, Year (Reference)	**Study Design**	**Numbers of Cases**	**Number of Noncases**	**Description of Association[a]**	**Strengths**	**Limitations**	**Other**
Watson et al., 1984 (26)	8 seasonal diseases from Minnesota; subjects born 1915–1959	3,246 cases[c]	Not reported	Association found for exposure to several viral infections, including diphtheria, pneumonia, and influenza	Earliest publication to investigate correlation between prenatal exposure to infection and observed seasonality of schizophrenia births	Used DSM-I and DSM-II diagnostic criteria; place of birth data unavailable; specific chi-square values not reported	Analyzed data on single and married case subjects both separately and in combination
Torrey, 1988 (27)	7 viral diseases in Conn. and Mass.; subjects born 1920– 1955	Conn.: 2,519 cases; Mass.: 5,007 cases; exposure status of individual cases not reported	Not reported	Measles: 5th–7th months; varicella zoster: 5th–7th months in Conn., but not Mass.		Diagnoses based on DSM-II criteria	Poliomyelitis associated with later schizophrenia in Conn. sample, but time lag between exposure and increased risk was 18 months
O'Callaghan et al., 1994 (28)	16 infectious diseases in England and Wales	12 regions in England and Wales: 6,982 cases; national cohort: 9,585 cases; exposure status of individual cases not reported	Not reported	Bronchopneumonia: 3rd–5th months; varicella zoster: 8th month; mumps: 6th month in national cohort, but not in 12-region cohort		Possible type I error due to multiple comparisons	Study used two independent sets of birth dates
Suvisaari et al., 1999 (29)	Poliovirus in Finland; subjects born 1959–1969	13,559 cases total; 4th month: 8,695 exposed cases, 4,075 unexposed cases; 5th month: 8,775 exposed cases, 4,134 unexposed cases; 6th month: 8,808 exposed cases, 4,232 unexposed cases	Not reported	Poliovirus: 4th–6th months; only 5th month remained significant after adjusting for season of birth (relative risk=1.05, 95% CI=1.00–1.11)	Obtained exact time and place of birth of patients and general population	Number of cases of paralytic poliomyelitis only approximates incidence of poliovirus infection in pregnant women	Poisson regression used to determine correlation between incidence of paralytic poliomyelitis and schizophrenia births
Cahill et al., 2002 (30)	Poliovirus in Australia; subjects born 1930–1964	6,078 cases; exposure status of individual cases not reported	Not reported	None		Register may overestimate case birth rates because the denominator covers only	

Authors, Year (Reference)	Study Design	Numbers of Cases	Number of Noncases	Description of Association[a]	Comments[b]		
					Strengths	Limitations	Other
						Queensland births, whereas the numerator includes cases born in other Australian states	

[a]Measures of effect (relative risk, rate ratio, or odds ratio) are reported here if reported in the original paper; p≤0.05 unless otherwise noted. "Nth month" indicates gestational month of exposure.

[b]All of the studies in the table share the following limitations: use of ecologic data and psychiatric registries to determine exposure and case status, respectively.

[c]Exposure status of cases not reported here because 15 different exposure categories were reported in the paper.

TABLE 3

Serological Studies of Prenatal Infection and Schizophrenia[a]

Cohort and Authors, Year (Reference)	Study Design	Numbers of Cases	Numbers of Noncases	Description of Association[b]	Comments: Strengths[c]	Comments: Limitations	Comments: Other
Collaborative Perinatal Project[d]							
Buka et al., 2001 (32)	Nested case-control study of numerous maternal infections, Providence, R.I., cohort followed up for psychotic disorders[e]	27 cases; dichotomous exposure status not provided because continuous measure of antibody was used	54 matched comparison subjects; dichotomous exposure status not provided because continuous measure of antibody was used	Elevated total maternal IgG and IgM and antibodies to HSV-2; no significant associations for IgA class immunoglobulins, IgG antibodies to HSV-1, cytomegalovirus, *T. gondii*, rubella, human parvovirus B19, *C. trachomatis*, or human papillomavirus type 16	Examined effects of many different infections to assess specificity	Small sample; for some subjects, maternal IgG levels included in analysis without having documented seropositivity	Broad definition of case sample including nonaffective and affective psychoses
Buka et al., 2001 (33)	Nested case-control study of maternal cytokines, Providence, R.I., cohort followed up for psychotic disorders[e]	27 cases; dichotomous exposure status not provided because continuous measure was used	50 matched comparison subjects; dichotomous exposure status not provided because continuous measure was used	Elevated maternal TNF-α: 3rd trimester; no significant associations for IL-1, IL-2, IL-6, but statistical trend for IL-8		Small sample	Broad definition of case sample including nonaffective and affective psychoses; 7 women were noted as having had an infection during the 3rd trimester and 6 during the 1st or 2nd trimester
Buka et al., 2008 (34)	Nested case-control study of HSV-2 from three birth cohorts (Boston, Providence, and Philadelphia) followed up for psychotic disorders[e]	62 seropositive cases, 138 unexposed cases	134 seropositive matched comparison subjects, 420 unexposed matched comparison subjects	Maternal HSV-2 seropositivity (odds ratio=1.6; 95% CI=1.1–2.3); risk was particularly elevated among women with high rates of sexual activity during pregnancy (odds ratio=2.6, 95% CI=1.4–4.6)	Large sample	Broad definition of psychosis including nonaffective (108 cases) and affective psychoses (85 cases)	Sera tested at end of pregnancy; diagnosis based on interview for New England cohorts and chart review for Philadelphia cohort
Child Health and Development Study[f]							
Brown et al., 2000 (35)	Birth cohort analysis of maternal respiratory	9 exposed cases, 49 unexposed cases	632 exposed noncases, 7,149 unexposed noncases	Maternal respiratory infection: 2nd trimester (rate ratio=2.13, 95% CI=1.05–4.35); strongest association for upper respiratory infections	Physician-based, prospective diagnoses of maternal	Broad measure of respiratory infection	

Cohort and Authors, Year (Reference)	Study Design	Numbers of Cases	Numbers of Noncases	Description of Association[b]	Comments		
					Strengths[c]	Limitations	Other
	infection[g] and DSM-IV schizophrenia spectrum disorders[h]				respiratory infection during pregnancy		
Brown et al., 2004 (36)	Nested case-control study of maternal cytokines and schizophrenia spectrum disorders[h]	59 cases; dichotomous exposure status not provided because continuous measure was used	105 matched comparison subjects; dichotomous exposure status not provided because continuous measure was used	Elevated maternal IL-8: 2nd–early 3rd trimester; no statistically significant association for IL-1β, IL-6, or TNF-α		Median TNF-α levels lower than in most studies of this cytokine	
Brown et al., 2004 (37)	Nested case-control study of influenza and schizophrenia spectrum disorders[h]	First half of pregnancy: 9 exposed cases, 34 unexposed cases; second half of pregnancy: 13 exposed cases, 51 unexposed cases	First half of pregnancy: 7 exposed and 68 unexposed comparison subjects; second half of pregnancy: 30 exposed and 95 unexposed comparison subjects	Influenza: first half of pregnancy (odds ratio=3.0, 95% CI=0.98–10.1); 1st trimester (odds ratio=7.0, 95% CI=0.7–75.3)	Influenza exposure was validated in a comparison sample with seroconversion data	Exposure based on proxy measure of seroconversion for influenza, but validated; marginally significant findings by standard criterion for significance (p=0.052 for first half of pregnancy exposure)	
Brown et al., 2005 (38)	Nested case-control study of *T. gondii* and schizophrenia spectrum disorders[h]	5 cases with "moderate" antibody titer, 13 cases with "high" antibody titer, 45 cases with reference titer (unexposed)	9 matched comparison subjects with "moderate" antibody titer, 13 with "high" antibody titer, 101 with reference titer (unexposed)	*T. gondii*: high IgG antibody titer (≥1:128) (odds ratio=2.61, 95% CI=1.00–6.82); no samples tested positive for IgM-specific *T. gondii* antibody indicating that acute infection was unlikely		Marginally significant finding by standard criteria (p=0.051)	Sera tested from 3rd trimester/ perinatal period
Babulas et al., 2006 (39)	Birth cohort study of maternal genital/ reproductive infection[i] and schizophrenia spectrum disorders[h]	71 cases; case/noncase status of exposed and unexposed pregnancies not reported	7,723 noncases; case/ noncase status of exposed and unexposed pregnancies not reported	Maternal genital/reproductive infections: periconceptional period (rate ratio=5.03, 95% CI=2.00–12.64)	Physician-based, prospective diagnoses of maternal genital/ reproductive infections; genital/ reproductive infection diagnoses from periconceptional period	Small sample of exposed cases (5 exposed)	
Brown et al., 2006 (40)	Nested case-control study of herpes viruses and schizophrenia spectrum disorders[h]	60 cases total; HSV-2: 16 exposed cases; HSV-1: 41 exposed cases; CMV: 43 exposed cases	110 matched comparison subjects total; HSV-2: 24 exposed comparison subjects; HSV-1: 70 exposed comparison	No association for IgG antibody level or seroprevalence of HSV-1, HSV-2, or CMV			Sera tested from 3rd trimester/ perinatal period

Cohort and Authors, Year (Reference)	Study Design	Numbers of Cases	Numbers of Noncases	Description of Association[b]	Comments: Strengths[c]	Comments: Limitations	Comments: Other
			subjects; CMV: 73 exposed comparison subjects				

[a] Ig=immunoglobin; HSV=herpes simplex virus; *T. gondii*=*Toxoplasma gondii; C. trachomatis*=*Chlamydia trachomatis*; TNF=tumor necrosis factor; IL=interleukin; CMV=cytomegalovirus.

[b] Measures of effect (relative risk, rate ratio, or odds ratio) are reported here if reported in the original paper; $p \leq 0.05$ unless otherwise noted. "Nth month" indicates gestational month of exposure.

[c] All of the studies in the table share the following strengths: direct biomarkers of infection obtained from archived maternal sera, population-based birth cohorts, diagnoses based on psychiatric interviews and medical chart reviews, and follow-up for psychosis/schizophrenia using specified protocols. The Child Health and Development Study featured two additional strengths: continuous follow-up and comparison subjects who were representative of the source population giving rise to cases.

[d] The Collaborative Perinatal Project was a multisite study of population-based birth cohorts throughout the United States. The table includes data from three birth cohorts from the project—those from Boston, Providence, R.I., and Philadelphia—on subjects born 1959–1967 who were followed up for psychotic disorders (schizophrenia, schizophreniform disorder, bipolar disorder with psychotic features, brief psychosis, and psychosis not otherwise specified); N=25,025 from 19,471 pregnant women for combined cohorts. All studies included here are nested case-control investigations of archived maternal serum analyzed for antibodies to infectious exposures.

[e] Psychotic disorders included schizophrenia, schizophreniform disorder, bipolar disorder with psychotic features, brief psychosis, and psychosis not otherwise specified. Diagnoses were established using both medical chart review and psychiatric interview (Structured Clinical Interview for DSM-IV).

[f] The Child Health and Development Study was a population-based birth cohort (N=12,094) in Alameda County, Calif., born 1959–1967 and followed up for schizophrenia and other schizophrenia spectrum disorders (schizophrenia, schizoaffective disorder, schizotypal personality disorder, delusional disorder, and "other schizophrenia spectrum psychoses") in adulthood in the Prenatal Determinants of Schizophrenia study (48). Two types of study designs were used. The first is cohort analytic designs in which classes of infections were defined on the basis of abstracted obstetric records; the second is nested case-control studies of archived maternal serum analyzed for antibodies to infectious exposures.

[g] Maternal respiratory infections included tuberculosis, influenza, influenza with pneumonia, bronchopneumonia, atypical pneumonia, pleurisy, emphysema/viral respiratory infections, acute bronchitis, and upper respiratory infections.

[h] Schizophrenia spectrum disorders included schizophrenia, schizoaffective disorder, schizotypal personality disorder, delusional disorder, and "other schizophrenia spectrum psychoses." Diagnoses were established using both psychiatric interview (Diagnostic Interview for Genetic Studies) and medical chart review.

[i] Maternal genital/reproductive infections included endometritis, cervicitis, pelvic inflammatory disease, vaginitis, syphilis, condylomata, "venereal disease," and gonorrhea.

TABLE 4

Other Birth Cohort Studies of Prenatal Infection and Schizophrenia

Authors, Year (Reference)	Study Design	Numbers of Cases	Numbers of Noncases	Description of Association[a]	Comments: Strengths	Comments: Limitations	Comments: Other
Crow et al., 1991 (41)	Retrospective assessment for influenza in a birth cohort born March 3–9, 1958, exposed to the 1957 A2 epidemic in England, Wales, and Scotland; cases identified via record search; diagnoses established by chart review (Present State Examination criteria)	16,268 total cases; exposed 1st trimester: 231 cases; exposed 2nd trimester: 945 cases; exposed 3rd trimester: 675 cases; number of unexposed cases not reported	Not reported	None	Large national sample; used individual pregnancies to determine exposure	Low statistical power; exposure to influenza determined from retrospective maternal interview	
Cannon et al., 1996 (42)	Retrospective assessment for influenza in pregnancies during 1957 A2 influenza epidemic in Ireland and later schizophrenia	2 exposed cases, 2 unexposed cases	236 exposed and 285 unexposed comparison subjects	None	Individual pregnancies	Exposure to influenza determined from retrospective maternal interview; low power due to small number of cases	Diagnoses made by chart review using the Research Diagnostic Criteria
Brown et al., 2000 (43)	Birth cohort study of rubella, based on physician diagnosis and/or rubella antibody titer, followed up for nonaffective psychosis[b]	11 exposed cases with nonaffective psychosis, 18 unexposed cases	42 exposed noncases, 1,526 unexposed noncases	Prenatal rubella exposure associated with increased risk of nonaffective psychosis (relative risk=5.2, 95% CI=1.9–14.3)	Rubella exposure was determined by either prospective clinical diagnosis or verification in a subsample by antibody titers; diagnoses based on psychiatric interviews	Lack of unexposed cases with verified rubella diagnoses; however, prenatal rubella was rare in the comparison cohorts	
Brown et al., 2001 (44)	Birth cohort study of rubella, based on physician diagnosis and/or rubella antibody titer, followed up for schizophrenia spectrum disorders[c]	11 exposed schizophrenia spectrum disorder cases, no unexposed cases	42 exposed noncases, no unexposed noncases	Prenatal rubella-exposed birth cohort evidenced a markedly high risk of schizophrenia spectrum disorder (11/53, 20.4%)	Diagnoses based on psychiatric interviews	No unexposed cohort to calculate effect size, although relative risk estimated at ~15-fold based on general population estimates of risk of	Cases included schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified, delusional disorder, schizotypal

Authors, Year (Reference)	Study Design	Numbers of Cases	Numbers of Noncases	Description of Association[a]	Comments: Strengths	Comments: Limitations	Comments: Other
						schizophrenia spectrum disorders; small sample size	personality disorder, and paranoid personality disorder
Mortensen et al., 2007 (45)	National cohort-based case-control study of *Toxoplasma gondii* combining data from national population registers and patient registers and a national neonatal screening biobank of filter paper blood spots in Denmark; subjects born after 1981 and followed up for schizophrenia through 1999	30 exposed cases, 41 unexposed cases	171 exposed and 513 unexposed comparison subjects	Elevated *Toxoplasma gondii* IgG anti-body (odds ratio=1.79, 95% CI=1.01–3.15)	Study compared risks for schizophrenia, schizophrenia-like disorders, and affective disorders; effect was specific to schizophrenia	Diagnoses based on psychiatric registry; partial ascertainment of eligible sample due to missing filter paper blood spots	Blood spots taken from infant; diagnoses based on psychiatric registry
Sørensen et al., 2009 (46)	Data from Copenhagen Perinatal Cohort, born 1959–1961 at Rigshospitalet in Copenhagen, linked with the Danish National Psychiatric Register for diagnoses of schizophrenia	32 cases exposed to any bacterial infection, 121 unexposed cases	1,033 noncases exposed to any bacterial infection, 6,755 unexposed noncases	Maternal bacterial infections[d]: 1st trimester, for both ICD-8 (odds ratio=2.53, 95% CI=1.07–5.96) and broadly defined schizophrenia (ICD-8 and/or ICD-10) (odds ratio=2.14, 95% CI=1.06–4.31); 2nd trimester, for ICD-8 (odds ratio=2.31, 95% CI=1.15–4.35) and broadly defined schizophrenia (odds ratio=1.82, 95% CI=1.06–3.14), only in unadjusted analysis		Diagnoses based on psychiatric registry; although exposures were based on clinical diagnoses, bacterial infections may have been misclassified; broad categories of infection (i.e., viral, bacterial); low statistical power	
Clarke et al., 2009 (47)	Data from Medical Birth Register linked with Finnish Population Register to identify women in Helsinki treated during pregnancy for upper urinary tract infection	36 cases exposed prenatally to upper urinary tract infection, 35 unexposed; 12 cases with a family history of psychosis, 59 cases	9,596 noncases exposed prenatally to upper urinary tract infection, 13,808 unexposed noncases; 1,497 noncases with a family history of psychosis, 21,907	No statistically significant association with prenatal infection alone, but observed interaction between prenatal exposure to upper urinary tract infection and family history (risk difference=0.51, 95% CI=0.06–0.96); 38%–46% of cases in sample may have	Large sample size; used sibling comparison group; hospital-treated infection provided exact information on time of exposure during pregnancy	Small number of cases; statistical power too low to examine each trimester separately	

Authors, Year (Reference)	Study Design	Numbers of Cases	Numbers of Noncases	Description of Association[a]	Comments		
					Strengths	Limitations	Other
	between 1947 and 1990; psychiatric out-comes of adult offspring identified through Finnish Hospital Discharge Register	with no family history	noncases with no family history	developed schizophrenia as a result of the synergistic action of both risk factors			

[a]Measures of effect (relative risk, rate ratio, or odds ratio) are reported here if reported in the original paper; $p \leq 0.05$ unless otherwise noted.

[b]Nonaffective psychosis was defined as 1) at least one psychotic symptom (delusions and/or hallucinations) for a minimum of 6 months; 2) no evidence of a major affective disorder (bipolar or unipolar) by DSM-III-R criteria concurrent with the psychosis; and 3) no evidence that a medical condition or substance use initiated or maintained the psychosis. Diagnoses were established using psychiatric interview (Diagnostic Interview Schedule for Children) and DSM-III-R criteria.

[c]Schizophrenia spectrum disorders included schizophrenia, schizoaffective disorder, schizotypal personality disorder, delusional disorder, and “other schizophrenia spectrum psychoses.” Diagnoses were established using both psychiatric interview (Diagnostic Interview for Genetic Studies) and medical chart review

[d]Maternal bacterial infections included sinusitis, tonsillitis, pneumonia, cystitis, pyelonephritis, bacterial venereal infection, and any other bacterial infection.

TABLE 5

Comparison of Histologic, Neuromorphologic, Neurocognitive, and Behavioral Outcomes Between Animal Models of Maternal Immune Activation (MIA), DISC1, and Neuregulin-1

MIA Model[a]	DISC1[b]	Neuregulin-1[c]
Histologic abnormalities		
Smaller, denser neurons in hippocampus; pyknotic cells in hippocampus	Reduced hippocampal gray matter volume and altered engagement of the hippocampus during several cognitive tasks in schizophrenia patients and healthy subjects with mutant DISC1 (72)	Hippocampal hypofunction and loss of interneurons (73)
Densely packed pyramidal cells; pyramidal cell atrophy	Defects in axonal targeting to CA3 pyramidal cells and development of synaptic outputs (74)	Decreased spine density on hippocampal pyramidal neurons (73)
Abnormal neuronal migration to layers II/III in cortex (unpublished, described in reference 56)	DISC1 suppression via RNAi resulted in abnormal neuronal migration to layers II/III in cerebral cortex (70)	Impaired thalamocortical migration (75)
Reduced NMDA receptor subunit 1 (NR1) expression in the hippocampus	No studies	Perfusion of neuregulin increased internalized NMDA receptor expression in cultured prefrontal cortex cells (76)
Reduced parvalbumin+ neurons in prefrontal cortex	Reduced parvalbumin+ neurons in medial prefrontal cortex. Parvalbumin+ cells displaced in dorsolateral frontal cortex (77)	Neuregulin receptor ErbB4 preferentially expressed by majority of parvalbumin+ interneurons in cerebral cortex (78)
Layer- and region-specific changes in the expression of SNAP-25	Decrease in SNAP-25 (71)	No studies
Delay in hippocampal myelination	Compromised DISC1 function in zebrafish disrupts oligodendrocyte development and results in myelination defects (69)	Hypomyelination (79)
Neuromorphologic abnormalities		
Ventricular enlargement	Mild ventricular enlargement in mice expressing mutant human DISC1 (80)	Ventricular enlargement (73)
Neurocognitive abnormalities		
Working memory deficit	Working memory and executive function deficits (81)	Working and short-term memory deficits (73); impaired recognition memory (82)
Behavioral abnormalities		
Latent inhibition deficit	Latent inhibition deficit, reversed with antipsychotic treatment (83)	Latent inhibition deficit (84)
Prepulse inhibition deficit, corrected with antipsychotic treatment	Prepulse inhibition deficit, corrected with antipsychotic treatment (83)	Prepulse inhibition deficit, corrected with chronic nicotine treatment (73)
Deficit in open field exploration	Hyperactivity in open field (males only) (71)	Increased baseline motor activity in open field (85)
Social interaction deficit	Alterations in social interaction (males only) (71)	Reduced social affiliative behavior (86); abnormal social dyadic interactions, including increased aggression (87)

[a]Reviewed in detail in Patterson (56).

[b]Findings are from mutant mouse model unless otherwise noted.

[c]Findings are from a heterozygous neuregulin-1 mutant mouse model unless otherwise noted.

TABLE 6

Effect Sizes and Attributable Proportions for Schizophrenia Following Prenatal Exposure to Selected Infections

Risk Factor	Odds Ratio or Relative Rate	Attributable Proportion
Influenza	3.0	14%
Elevated toxoplasmosis IgG antibody	2.6	13%
Periconceptional genital or reproductive infection[a]	5.0	6%

[a]Maternal genital or reproductive infections include endometritis, cervicitis, pelvic inflammatory disease, vaginitis, syphilis, condylomata, “venereal disease,” and gonorrhea.