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The environment and susceptibility to schizophrenia

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Abstract

In the present article the putative role of environmental factors in schizophrenia is reviewed and synthesized. Accumulating evidence from recent studies suggests that environmental exposures may play a more significant role in the etiopathogenesis of this disorder than previously thought. This expanding knowledge base is largely a consequence of refinements in the methodology of epidemiologic studies, including birth cohort investigations, and in preclinical research that has been inspired by the evolving literature on animal models of environmental exposures. This paper is divided into four sections. In the first, the descriptive epidemiology of schizophrenia is reviewed. This includes general studies on incidence, prevalence, and differences in these measures by urban–rural, neighborhood, migrant, and season of birth status, as well as time trends. In the second section, we discuss the contribution of environmental risk factors acting during fetal and perinatal life; these include infections [e.g. rubella, influenza, *Toxoplasma gondii* (*T. gondii*), herpes simplex virus type 2 (HSV-2)], nutritional deficiencies (e.g., famine, folic acid, iron, vitamin D), paternal age, fetal/neonatal hypoxic and other obstetric insults and complications, maternal stress and other exposures [e.g. lead, rhesus (Rh) incompatibility, maternal stress]. Other putative neurodevelopmental determinants, including cannabis, socioeconomic status, trauma, and infections during childhood and adolescence are also covered. In the third section, these findings are synthesized and their implications for prevention and uncovering biological mechanisms, including oxidative stress, apoptosis, and inflammation, are discussed. Animal models, including maternal immune activation, have yielded evidence suggesting that these exposures cause brain and behavioral phenotypes that are analogous to findings observed in patients with schizophrenia. In the final section, future studies including new, larger, and more rigorous epidemiologic investigations, and research on translational and clinical neuroscience, gene–environment interactions, epigenetics, developmental trajectories and windows of vulnerability, are elaborated upon. These studies are aimed at confirming observed risk factors, identifying new environmental exposures, elucidating developmental mechanisms, and shedding further light on genes and exposures that may not be identified in the absence of these integrated approaches. The study of environmental factors in schizophrenia may have important implications for the identification of causes and prevention of this disorder, and offers the potential to complement, and refine, existing efforts on explanatory neurodevelopmental models.

Keywords

Environmental; Schizophrenia; Epidemiology; Cohort; Birth cohort; Ecologic; Incidence; Prevalence; Neurodevelopment; Risk factors; Exposures; Prenatal; Maternal; Maternal fetal; Pregnancy; Fetus; Fetal; Determinants; Attributable proportion; Infection; Influenza; Rubella;

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Toxoplasma gondii; *T. gondii*; Herpes simplex; HSV2; Cytokines; Nutrition; Protein deprivation; Famine; Malnutrition; Micronutrient; Folate; Folic acid; Homocysteine; Iron; Vitamin D; Hypoxia; Obstetric complications; Lead; Rhesus incompatibility; Rh incompatibility; Stress; Socioeconomic status; Trauma; Cannabis; Migrant; Psychosocial; Urban; Urban rural; Urbanicity; Season of birth; Seasonality; Animal models; Maternal immune activation; Poly I:C; LPS; Gene-environment interaction; Epigenetics; Microarray; Copy number variants; CNV; Dopamine; Glutamate; NMDA; GABA; Developmental trajectories; Pathogenic models; Prevention; Genetics; Translational

1. Introduction

In the present article, we seek to provide a comprehensive review of, and cast new light on, the role of the environment in the origins of schizophrenia. Although earlier work provided suggestions that environmental factors are of potential relevance to schizophrenia, methodologic limitations, and the lack of biological models, limited the extent to which pertinent hypotheses could be tested and refined. In recent years, however, the role of the environment in susceptibility to schizophrenia has garnered increased attention. This has come about mainly as a result of three recent developments. First, several birth cohort studies with large prospectively collected databases on prenatal and perinatal risk factors, have matured into the age of risk for schizophrenia. Second, concerted efforts have been made to improve upon data collection methods in order to systematically identify and test for a number of risk factors during childhood and adolescence in relation to risk for the disorder. Third, translational studies of schizophrenia have begun to incorporate measures of the environment into animal models.

In our view, environmental factors need to be considered as etiologies of neuropsychiatric disorders including schizophrenia, given that they have been well-established to cause or contribute to a large number of medical conditions. In fact, most of the major initiatives that have led to a decline in incidence of disease in modern times related to interventions aimed at reducing exposure to environmental risks. As examples, anti-smoking campaigns and other measures have led to an appreciable reduction in risk of lung cancer in countries which promulgated these interventions (Samet, 1994), the successful eradication of many infectious agents in many though not all regions of the world has been clearly shown to reduce infant and childhood morbidity and mortality (Stoll, 2006), and routine folate supplementation, now introduced in several countries, has brought about a marked decrease in risk of neural tube defects (Scott et al., 1995). Environmental exposures, including infections, nutritional deficits, and neurotoxins, are known causes of neuropsychiatric disorders, and are potent disruptors of brain development, which has been proposed to play a major role in the etiology of schizophrenia (Brown et al., 2005a).

To date, however, the search for genetic mutations has dominated discourse on etiologies of schizophrenia. This is perhaps not surprising, given that twin, family, and adoption studies, which date back many decades, all clearly support a major role for genes in schizophrenia (Riley et al., 2005). The strongest of these findings derives from studies demonstrating that the concordance rate of schizophrenia for monozygotic (MZ) twins is approximately 45–60%, compared to a rate of 10–15% for dizygotic twins. The fact that is less frequently discussed, however, is the 40–55% discordance rate for schizophrenia cases who share identical genes. Although stochastic mechanisms have been invoked to account for this high rate of discordance, the most plausible explanation is for a role of environmental factors. Such factors may operate as early as the in utero period, given that the fetal experience even of MZ twins can differ (Piontelli et al., 1999).

Heritability studies, which are based on twin concordance and discordance rates have contributed to the assertion that schizophrenia is largely a genetic disorder, with environmental exposures playing only a minor role. Heritability has been formally defined as the proportion of total variance that is attributable to variation in additive or total genetic values, or in other words the fraction of variation between individuals in a population resulting from their genotypes (Visscher et al., 2008). Typical heritability estimates for schizophrenia are approximately 80% (Sullivan et al., 2003). However, these estimates represent an imperfect measure of the respective roles of genetic and environmental contributions, as previously elaborated by Schwartz and Susser (2006), which has the potential to underestimate the role of the environment. First, genes that operate to increase risk of a disorder by altering the environment are included in the genetic component in the heritability model. Second, gene–environment interaction, which likely plays an important role in the etiology of schizophrenia, cannot be meaningfully evaluated in a twin design, because such interactions are counted only as part of the genetic contribution to the variance. These two points are based on how genetic and environmental contributions are calculated in the standard twin study model, which is not based on direct measurement of environmental factors, but rather on the proportion of unexplained variance that remains once “genetic” effects are taken into account. Hence, it is plausible, and perhaps likely, that heritability models produce an underestimate in the contribution of environmental factors to risk of this disorder.

Another reason that the environment has received less attention than genes is the difficulty in measuring this construct and in relating environmental measures to risk of schizophrenia. However, new epidemiologic designs have been implemented that offer substantial improvements on the measurement and timing of relevant environmental exposures and the introduction of additional methodologic advances. These designs will be discussed below.

In this review, we shall first discuss the descriptive epidemiology of schizophrenia, including the distribution of the disorder by place, and the evaluation of temporal variation. We shall then review the literature on putative biologically and psychosocially based risk factors for this illness. In the next section, we will synthesize these findings and discuss their implications for prevention and refinement of a neurodevelopmental framework for schizophrenia. Finally, we shall elaborate upon future directions considered necessary to refine and expand upon our understanding of the role of environmental factors in the susceptibility to schizophrenia.

2. Descriptive epidemiology

The descriptive epidemiology of a disorder can provide valuable clues as to its origins. Studies of etiologies of illness often begin with the description of the spatial and temporal distributions of the disorder.

Epidemiologic studies focused on spatial distribution encompass overall incidence and prevalence, their comparison between societies, and relationships between occurrence of the illness and demographic subgroups defined by place or other population characteristics (Rothman and Greenland, 1998). Epidemiologic studies of temporal distribution evaluate whether changes in incidence or prevalence occur over particular intervals of time. Variations in the occurrence of schizophrenia by place or time are indicative of environmental etiologies, since genetic differences are unlikely to explain such effects. While these studies only rarely lead to the isolation of specific environmental determinants, they do allow for the generation of testable hypotheses regarding putative risk factors, in addition to their important role in the allocation of resources for intervention.

2.1. Spatial distribution

In this section, we summarize data from previous studies on incidence and prevalence of schizophrenia throughout the world. We then discuss studies that have compared populations based on particular demographic characteristics that vary in spatial distribution, including urbanicity, immigration status, and neighborhood effects.

2.1.1. Incidence of schizophrenia—Incidence is defined as the number of new cases in a population over a period of observation (Rothman and Greenland, 1998). In a recent review of over 150 studies drawn from 33 countries McGrath et al. (2004) reported on incidence data for schizophrenia from 1965 to 2001. The mean incidence rate was 15.2 per 100,000 and the range was 7.7–43.0 per 100,000. While at least some of the difference in rates can be attributed to variations in diagnostic classification and ascertainment between studies, these findings nonetheless indicate that there may be more significant variation in incidence of schizophrenia than has been previously recognized. The finding on overall incidence is remarkably similar to that of the landmark World Health Organization (WHO) 10 Nation study, which implemented uniform methodology across sites (Jablensky et al., 1992). Using two different diagnostic systems, that study reported a range of incidence from as low as 14 per 100,000 to as high as 42 per 100,000.

Overall, the incidence of schizophrenia was found to be higher in males than females (McGrath et al., 2004). The ratio of incidence rates between men and women was 1.4 (Aleman et al., 2003).

2.1.1.1. Incidence differences between developed and developing countries: Given the variation in incidence rates described above, it is worth considering whether the examination of differences in incidence between developing and developed countries may help inform the role of environmental etiologies of the illness. In particular, these findings can point to sociocultural differences that may influence risk of this disorder. While there has been a persistence of the notion that the incidence is the same or similar between countries, the epidemiologic data generally do not accord with this view.

In the WHO Ten Country Study discussed above, which included assessments of the incidence of schizophrenia in both developed and developing countries, there were numerical differences in incidence rates, but no significant variation between countries, when schizophrenia was defined by narrow criteria (Saha et al., 2005). However, when a broad definition of schizophrenia was used, the developing countries had higher incidence rates than the developed countries. Although the study did not examine specific risk factors, this provides a potential clue suggesting that certain environmental factors common to developing countries may influence the risk of schizophrenia, at least under the broad definition used in that study.

2.1.2. Prevalence of schizophrenia—Prevalence is a measure of the proportion of subjects in a population with a disorder, either at a specified time (point prevalence) or over a specified period (period prevalence) (Gordis, 2000). Lifetime prevalence is the proportion of subjects in a population who have ever been diagnosed with a disorder, and who are in the population on a given day. In a review of prevalence studies over nearly the same years as in the incidence paper reported above, Saha et al. (2005) found that the median point prevalence, and lifetime prevalence estimates were 4.6 per 1,000 and 4.0 per 1,000, respectively.

2.1.3. Differences in risk by urban versus rural birthplace, residence, and neighborhood

2.1.3.1. Urban–rural findings: Many studies have demonstrated an increased risk of schizophrenia among individuals living in urban, compared to rural areas. This raised the question of whether such factors were due to selective migration, to factors operating during early life, or those influencing risk later in life. To address this question, several population-based cohort studies have been conducted. These studies have uniformly demonstrated that being raised in an urban area, compared to a rural area, confers a greater risk of schizophrenia (Marcelis et al., 1999; March et al., 2008a; Mortensen et al., 1999). Approximately one third of all such studies reported a “dose–response” relationship between level of urbanicity and psychosis (March et al., 2008a), including one particularly large study from Denmark of urbanicity at birth and risk of schizophrenia, with approximately a two-fold increased risk among individuals born in the capital compared to rural regions (Mortensen et al., 1999). In a study from the Netherlands which attempted to disentangle place of birth from place of residence, Marcelis et al. (1999) demonstrated no relationship between urban residence at the time of onset and schizophrenia risk following adjustment for place of birth. The question of the timing of the effect of place of birth was further investigated by comparing the relative effects of being born versus raised in an urban area on risk of schizophrenia (Pedersen and Mortensen, 2001). In this extensive study from Denmark on the effects of urbanicity that made use of data on changes of residence among individuals at successive ages, during birth and at several points during childhood and adolescence, the authors reported two main findings. First, the greater number of years lived in the areas with higher degrees of urbanization, the greater the risk of schizophrenia. Hence, based on their data, the cumulative amount of “urban living” was a clear factor that contributed to risk of the disorder. Second, following mutual adjustment of urbanicity at birth and during upbringing (up to age 15), the effect of urbanicity during upbringing remained highly significant, while the effect of urbanicity at birth was no longer present. These findings provided support for being raised, but not born in an urban area, as a risk factor for schizophrenia. The urban–rural question was further explored by these authors in a study which compared individuals and their nearest older sibling's risk of schizophrenia in relation to place of birth (Pedersen and Mortensen, 2006). The essential finding of this study was that an individual's place of birth and upbringing, and nearest older sibling's place of birth, both contributed to risk of schizophrenia, suggesting that both family-level and individual-level exposure to the urban risk factor are important variables to consider.

As noted below (see Section 4.1), the population attributable risk for development of schizophrenia ascribed to birth in an urban environment is considerable, approximately 30% (Marcelis et al., 1998; McGrath and Scott, 2006; Mortensen et al., 1999).

2.1.3.2. Neighborhood effects: In an extension of this work, two studies examined the role of social context of the neighborhoods in which individuals live on the relationship between immigrant status and incidence of schizophrenia. Boydell et al. (2001) in London, in a study of case records over a 10-year interval, found a “dose–response” relationship between increasing incidence of schizophrenia in ethnic minorities concurrent with a decline of the proportion of minorities in the neighborhoods. Veling et al. (2008), in a prospective first-contact incidence study of psychotic disorders in the Hague, reported an increased incidence rate ratio of psychotic disorders among immigrants living in neighborhoods in which their own ethnic group represented a small proportion of the population of that neighborhood (termed “low ethnic density”), compared to those neighborhoods in which they represented a high corresponding proportion of the population (“high ethnic density”). These findings suggest that the social context can modify the effect of individual-level risk factors, in this case, ethnicity and immigrant status. Although there are a number of potential explanations,

one attractive interpretation is that living in a neighborhood with a larger proportion of those of the same ethnicity may alleviate potential effects of discrimination on risk of schizophrenia. This is consistent with previous findings that the experience of discrimination may be associated with an increased risk of schizophrenia and psychotic symptoms (Veling et al., 2007).

2.1.3.3. Specific environmental factors that may explain these findings: These findings may have particular relevance to the identification of specific risk factors, in that they suggest that environmental factors common to urban regions and linked to schizophrenia could account for them. The potential list, however, is long, and includes vitamin D, which has clear urban–rural gradients (Nesby-O'Dell et al., 2002) (see Section 3.1.4.2.3); microbial pathogens (see Section 3.1.3), which may be found at higher rates in individuals who are subjected to crowded living conditions; toxins, such as exposure to leaded gasoline (see Section 3.1.7.1); diet (see Section 3.1.4); and a variety of sociocultural factors. With regard to the urbanicity risk factor, recent interest has particularly arisen with regard to social capital and social fragmentation (March et al., 2008a; McGrath and Scott, 2006). Social capital involves characteristics at the community level, such as “connectedness” and positive support, that facilitate participation for reciprocal benefit. Social capital has been inversely related to the incidence of psychosis, adjusting for individual-level variables and neighborhood-level deprivation (Kirkbride et al., 2007; Lofors and Sundquist, 2007). Social fragmentation is another construct that is associated with urban life, particular in the inner cities, that has been associated with an increased risk of schizophrenia (Allardyce et al., 2005). This involves disorganization and instability among communities, characterized by social isolation and poor communication among the inhabitants (Faris and Dunham, 1939; Park et al., 1925).

In a recent review of 44 studies of urbanicity/neighborhood and psychosis, March et al. (2008a) expand these constructs further into a theory that places greater emphasis on “place,” versus “space.” Building on an argument that is based on the question of how exposure to the urban environment might produce variation in schizophrenia risk, the authors suggest that a focus on key social pathways by which salient exposures are created and maintained, could unravel the complexity of the urban/neighborhood risk factors. By “social pathways,” the authors are referring to “cascades of social processes across multiple levels that produce a variety of conditions in a given place, which shape exposures more proximal to the individual (March et al., 2008b).” Central to this argument is the concept of “place,” which includes the natural and built environment within a designated geographic location. These overarching environmental structures could give rise to a multitude of social, economic, and biological risk factors which interact with one another at different levels, thereby increasing schizophrenia risk. As an example, urbanization can produce crowding, which might increase the likelihood of transmission of infectious agents, which have been associated with schizophrenia (Section 3.1.3). In a second example, “structural discrimination” could lead minority groups and individuals in low socioeconomic strata to move to neighborhoods with unhealthy living conditions, such as environments with greater levels of toxic exposures, or not allow them to move from a community in which such exposures are being created, such as those populated by landfills, new highways, or proliferation of “crackhouses.” Through this mechanism, community-level exposures can create the conditions for individual-level exposures, and the combination of macrostructural and microstructural exposures act to increase liability to schizophrenia.

2.1.4. Incidence of schizophrenia and migrant populations—Migration has been demonstrated to be a risk factor for schizophrenia (for review see Cantor-Graae and Selten, 2005). Elevated incidence rates of schizophrenia have been found in many studies of migrant populations. These include individuals of African Caribbean background in the

United Kingdom, people of Surinamese, Dutch Antillean, and Moroccan background in the Netherlands, and several migrant groups in Denmark (Cantor-Graae and Selten, 2005). This hypothesis was first proposed by Odegaard (1932), who demonstrated that the incidence rate of first admissions for schizophrenia in Norwegian immigrants to the USA was double the rate in native-born Americans and Norwegians who resided in Norway. While Odegaard argued that the findings were due to selective migration, more recent studies have evaluated whether this is indeed the case, or whether other explanations, including environmental factors, may play a role (Cantor-Graae and Selten, 2005).

One of the most comprehensive reviews on this topic is by Cantor-Graae and Selten (2005). Their meta-analysis involved eighteen studies, consisting of first-contact incidence studies, hospital-based first-admission studies, and national register studies. The studies were conducted in Australia, the Netherlands, the United Kingdom, Denmark, and Sweden. For first-generation migrants, the authors found a mean (weighted) relative risk of 2.7 [95% confidence intervals (CI) = 2.3–3.2], indicating a nearly threefold overall increased risk of schizophrenia among this group. For second-generation migrants, the mean relative risk was 4.5 (95% CI = 1.5–13.1). In the largest dataset, which included studies that did not distinguish first and second-generation migrants, the mean relative risk was 2.9 (95% CI = 2.5–3.4). Only minor differences were found when the studies were re-grouped by the method of diagnosis. Migrants from developing countries had greater risks compared to migrants from developed countries.

A key question raised is whether skin color played a role in these findings. When the studies were re-analyzed based on this factor, the risk of schizophrenia was found to be nearly five-fold higher if the migrants emigrated from countries with predominantly black populations. This figure was twice as high as the elevated risk found among white or non-white/non-black migrant populations. Similar findings, of a greater risk of schizophrenia in black, compared to other immigrants, have been reported in additional studies (Dealberto, 2010). Based on the work of McGrath and colleagues (see Section 3.1.4.2.3), the authors speculated that the markedly higher rates of schizophrenia in black immigrants, compared to their native countries, may be explained by vitamin D deficiency. Circulating vitamin D levels are lower in black, compared to non-black populations (Holick et al., 1995) and decreased sun exposure due to adaptation of black immigrants to the Western way of life, which includes Western-style clothing and living and working indoors, is an attractive explanation for the differences between the prevalence of schizophrenia in African countries and in black immigrants to Western countries (Dealberto, 2010).

These findings do not appear to be explained by diagnostic bias or by an increased likelihood of migrants to seek or end up in treatment for other reasons. With regard to Odegaard's conclusion regarding selective migration of individuals predisposed to schizophrenia (Odegaard, 1932), the evidence suggests that this argument may not be valid. First, in the findings from the Netherlands, one-third of the Surinamese population emigrated. Furthermore, the premorbid or prodromal characteristics of individuals who later develop schizophrenia may create an obstacle to migrate, or make it more likely that they will require the support of family or other caregivers in their place of birth.

Cantor-Graae and Selten (2005) and others have offered possible explanations for migration as a risk factor for schizophrenia. These include discriminatory experiences, a mechanism which is consistent with the particularly high rate of schizophrenia among migrants with black skin. This finding is consistent with the observation of a two-fold elevated risk of schizophrenia among African-Americans in a birth cohort study in the USA (Bresnahan et al., 2007). Other possible explanations include ethnic disadvantage, which can interfere with creating goals and objectives that allow an individual to adapt to the society and the

experience of social defeat, a chronic stressful condition. The urban risk factor should also be considered as a possible explanation. As noted by Cantor-Graae and Selten (2005), in order for the effect of the migrant risk factor to be explained by urbanicity, migrants would need to be either more intensively exposed or more sensitive to urbanicity. Another possibility is that the increased effect of migrant status on schizophrenia risk is due to cannabis. However, several findings, discussed in Cantor-Graae and Selten (2005), argue against this. First, the approximately two-fold increase in overall risk related to cannabis is smaller than the effect size found in studies of migration. Second, cannabis use occurs at higher rates in males, but no sex differences in the migration effect on schizophrenia have been found. Third, increased rates of illegal drugs have not been observed in migrant studies of schizophrenia.

2.2. Temporal variations

Studies which are aimed at examining changes in incidence of schizophrenia over time could reveal environmental factors that play etiologic roles if the increased incidence is shown to be correlated with the introduction or increase of an environmental agent in a population.

A number of studies have reported a decline in the incidence of schizophrenia in industrialized countries, beginning in the 1950s (Suvisaari et al., 1999b). These include studies in Great Britain, continental Europe, and Australia. The findings are not entirely consistent, however, as the rate of first-admission for schizophrenia has not decreased in Croatia, the Netherlands, and parts of England. One study, in south-East London, demonstrated that the rate of first admission/treatment contact for schizophrenia increased nearly two-fold from 1965 to 1997 (Boydell et al., 2003). It is unclear, however, whether changes in incidence of schizophrenia, either increasing or decreasing, in these studies are related to alterations in population demographics or to changes in diagnostic practices.

In one of the most comprehensive papers on this topic, Suvisaari et al. (1999b) examined changes in the incidence of schizophrenia in Finland using national birth and treatment registries, among individuals born between 1954 and 1965. A significant decline in the incidence of schizophrenia was observed for each successive year of birth. There were two key advantages to this study. First, the investigators capitalized on the fact that this was a birth cohort study. Given that year of birth was known, they were able to differentiate whether changes in risk were related to birth year or to the period in which the diagnosis was made, which can be especially prone to confounding by changes in diagnostic practice. Second, they capitalized on national psychiatric registries, which included most cases of clinically diagnosed schizophrenia in the country. Their results demonstrated a decline in incidence of schizophrenia in successive birth cohorts even after adjusting for the period of years in which the diagnoses were made. These findings suggest that the decline in incidence could reflect the effect of risk factors operating in early life, such as improvements in obstetric care and decreased risk of infections during pregnancy.

2.2.1. Season of birth—One of the best replicated findings in epidemiologic research on schizophrenia is the association between birth during the winter and early spring. Subjects born during this period have a 5–15% increase in risk of schizophrenia (Bradbury and Miller, 1985; Davies et al., 2003; Torrey et al., 1997), and there is a similar decline in schizophrenia risk among subjects born during the autumn months. An intriguing association has also been demonstrated between birth during the summer months and the occurrence of the deficit syndrome of schizophrenia, which is defined as persistent negative symptoms that are not secondary to medication (Kirkpatrick et al., 1998). These findings

provide evidence that environmental factors which correlate with season may influence risk of schizophrenia (see Section 3).

3. Risk factor studies of schizophrenia

3.1. Risk factors during early life

3.1.1. Neurodevelopmental origins of schizophrenia—Accumulating evidence from epidemiologic, clinical, and basic neuroscience research suggests that schizophrenia is primarily a neurodevelopmental disorder. Prospective studies of offspring who later develop schizophrenia have revealed a tendency for impaired neurocognitive (Cannon et al., 2002b; David et al., 1997; Jones et al., 1994b; Niendam et al., 2003; Reichenberg et al., 2002), behavioral (Brown et al., 2001; Cannon et al., 2002a; Done et al., 1994; Jones et al., 1994b), and neuromotor function (Cannon et al., 2002b; Murray et al., 2006; Rosso et al., 2000; Walker et al., 1994). Patients with schizophrenia also have an increased prevalence of minor and major physical anomalies, especially of the craniofacial area, which are indicative of an in utero developmental disruption (Lloyd et al., 2008; McGrath et al., 2002; Waddington et al., 2008; Waddington et al., 1999). Moreover, MRI studies of first episode cases of schizophrenia have revealed morphologic brain abnormalities, including ventricular enlargement (Lawrie and Abukmeil, 1998; Vita et al., 2006; Wright et al., 2000), decreased hippocampal volume (Bogerts et al., 1990; Nelson et al., 1998; Ward et al., 1996), and an increased prevalence of cavum septum pellucidum (CSP) (Degreef et al., 1992; DeLisi et al., 1993; Kwon et al., 1998; Nopoulos et al., 1997). CSP is a neuroembryologic marker, given that it arises from incomplete closure of the septal leaflets in the midline of the brain before the first 6 months of life, indicating that it is a consequence of a brain maturational disruption during the in utero period or early infancy (Farruggia and Babcock, 1981).

Two major initial epidemiologic clues for a neurodevelopmental origin to schizophrenia have already been discussed. These include the associations between schizophrenia and both season of birth and urban birth (see Sections 2.1.3 and 2.2.2). Season of birth could be relevant to in utero infection or possibly other fetal environmental exposures given that the incidence of many infections and other environmental factors have seasonally varying patterns. Urban birth could also reflect fetal environmental exposures that are common to cities, including pollutants and possibly infections given that higher population density may predispose to the spread of infectious microbes, increasing the likelihood of exposure during pregnancy.

These studies provided an empirical basis for the generation of hypotheses on environmental exposures that are known causes of congenital brain and behavioral anomalies as potential risk factors for schizophrenia. Rigorous testing of these factors required epidemiologic research designs. Before reviewing these studies, we wish to describe the types of research designs used in epidemiology to substantiate associations between prenatal environmental factors and risk of schizophrenia.

3.1.2. Epidemiologic research designs on fetal and perinatal exposures—Two major research designs have been employed. The first are *retrospective* designs (Gordis, 2000). In these studies, a sample of schizophrenia cases are collected from a particular source, most commonly hospital records. Information is obtained on potential risk factors from archived sources, including birth certificates, anamnestic reports from the mother, or a combination of these approaches. While these studies offer the potential to provide important initial data linking environmental exposures during the prenatal, and peri-/neonatal periods with risk of disorder, they are also potentially compromised by a number of limitations. First, the samples collected represent select cases who are drawn to a particular treatment setting, and may therefore not be representative of the population from which they

are drawn, which can create bias and limit generalizability. Second, the information collected, even if obtained prior to onset of the disorder, is generally not systematically collected and is often limited with regard to the range and precision of the exposures. Third, studies that have utilized maternal recall of events during pregnancy collected after schizophrenia is diagnosed have the potential to lead to biased reporting, since mothers who have offspring with the disorder may be more likely to remember obstetric complications and other events during pregnancy than mothers of control offspring. Moreover, such reporting is fraught with the potential for imprecision; for example, a mother may report that she had “flu” during pregnancy, but this could have been influenza, an upper respiratory infection, or even a gastrointestinal disturbance.

In contrast, *cohort* studies offer much greater potential for yielding valid data on exposure-outcome measures. In a retrospective *cohort* study, archival records based on exposures and outcomes in a cohort are obtained and exposure-outcome relationships are assessed (Gordis, 2000). Since these studies make use of existing cohorts, exposure data were prospectively and systematically collected on the exposures at the time of their occurrence. These studies generally rely on available electronic databases, or registries, to obtain data on outcomes, such as schizophrenia, among members of the cohort who were followed up. A variation of a retrospective cohort study relies upon exposure data based on a documented population-based exposure, such as an epidemic. The data derived from these studies are termed *ecologic*.

The most robust design to examine fetal and perinatal determinants of illness is the *birth cohort study*. A birth cohort is a group of individuals who are born during a specified period and at a specified geographic region or regions. In birth cohort studies, representative samples of pregnancies are recruited from the population and data are collected by specified protocols including assessment of demographics, health habits, prior pregnancies, maternal conditions during pregnancy, routine pregnancy measures, and prescribed medications. In some of these studies, biospecimens, including maternal and cord sera and neonatal filter paper blood spots, are collected and archived for future use. Cohort studies have four major advantages over retrospective studies. First, data are systematically collected specifically for research purposes, ensuring much greater uniformity and precision of the data. Second, since the exposure data are obtained long before the schizophrenia outcome, these data cannot be biased by the outcome. Third, the use of archived maternal or neonatal specimens permits the examination of biomarkers of in utero exposures that were not hypothesized or collected at the time of the pregnancies. Fourth, the comprehensive data collected from the pregnancies and offspring more readily allows for adjustment of potential confounding or interacting factors.

3.1.3. Prenatal exposure to infection—In this section, we review previous studies on relationships between prenatal infection and risk of schizophrenia. Since these studies have been reviewed extensively elsewhere, a summary table is not provided; rather, the reader is referred to a comprehensive review of this topic (Brown and Derkits, 2010). Infection is considered to be a plausible candidate environmental risk factor for schizophrenia, as it has long been known that infectious microbes cause congenital brain anomalies, neurocognitive dysfunction, and behavioral disorders. Fetal exposure to rubella, herpes simplex virus, toxoplasmosis, syphilis, and other infections lead to neuropsychiatric disturbances such as mental retardation, learning disabilities, sensorineural problems, and neuromorphological anomalies (Remington and Klein, 2006).

3.1.3.1. Studies based on ecologic exposure data: Studies that employed ecologic data on infection allowed investigators to investigate the relationship between specific infections and schizophrenia. In these studies, the exposure was defined as the timing of an infectious

epidemic in a population. This exposure was examined in relation to the dates in which individuals who later developed schizophrenia, and those who did not, were expected to have been *in utero*. Influenza was among the first of these infections that were studied, since it is relatively common in the population and influenza epidemics are systematically recorded in developed countries.

Two research designs were employed. The first design focused on a single epidemic, most commonly the 1957 type A2 influenza pandemic. This epidemic was selected due to its high morbidity and the circumscribed period of its occurrence. In the second design the exposure was enumerated by variations in incidence of influenza based on records of epidemics over long intervals. Both types of studies capitalized on psychiatric registries, either from entire countries, or regions within countries, containing diagnoses of schizophrenia. By relating the dates of birth of schizophrenia cases and non-cases with the periods of the epidemics, it was possible to identify when an epidemic occurred in relation to trimesters or months of gestation of the individuals.

In the initial reports, associations were observed between influenza epidemics during all or part of the second trimester and schizophrenia among offspring exposed to the epidemics at that time during fetal life (Brown and Derkits, 2010). The first of these studies, conducted in Finland, demonstrated that subjects who were in the second trimester of fetal development during the 1957 type A2 influenza epidemic had a significantly increased occurrence of schizophrenia than subjects who were not in utero during the second trimester (Mednick et al., 1988). That study was limited, however, by outcome data reported as a proportion of cases with schizophrenia among all hospitalized cases with psychiatric disorders. However, subsequent studies of this epidemic, which used population denominators, replicated the finding. This included work from Great Britain (Kendell and Kemp, 1989; O'Callaghan et al., 1991), Japan (Kunugi et al., 1995), and Australia (McGrath and Castle, 1995). Studies that included measures of effect generally demonstrated approximately two-fold increases in risk. Other studies that attempted to relate the annual prevalence of influenza epidemics over many decades have largely confirmed these results (Adams et al., 1993; Barr et al., 1990; Sham et al., 1992; Takei et al., 1993). There have, however, been several studies that failed to replicate these associations, including studies with some notable methodologic strengths, including more thorough case ascertainment and relatively large numbers of cases (Erlenmeyer-Kimling et al., 1994; Susser et al., 1994; Westergaard et al., 1999).

In a recent meta-analysis of the studies based on the 1957 influenza pandemic, Selten et al. (2010) found, in weighted results, no significantly increased risk of schizophrenia from exposure during any gestational month of trimester. The included studies were nearly all based on ecologic definitions of exposure.

Studies that utilized ecologic data on other infections, including maternal respiratory viral infections (O'Callaghan et al., 1994; Watson et al., 1984), measles (Torrey, 1988), varicella-zoster (O'Callaghan et al., 1994; Torrey, 1988), and polio (Suvisaari et al., 1999a) have also revealed associations with schizophrenia in offspring.

The lack of replications in the studies of influenza may have been due to methodologic limitations. The most significant of these limitations is the potential misclassification of exposure because, as noted above, subjects were deemed “exposed” based on the timing of epidemics in populations (as per the ecologic design); however, even during the most severe epidemics including the 1957 type A2 epidemic, the incidence was approximately 25% of the population for the period of exposure classified in these studies, meaning that misclassification of exposure occurred in most subjects in these studies (Henderson et al., 2009). In addition, some proportion of subjects who were classified as unexposed would

have been exposed since not all influenza would have been acquired during epidemic periods. A second limitation of these studies is the assumption of a full-term pregnancy, which would result in inaccurate gestational timing of the exposure (Mednick et al., 1988). Both of these limitations would have biased the findings toward the null, potentially explaining the inability to replicate positive findings. Other limitations included incomplete ascertainment of the source population, lack of population denominators representing births, less systematic diagnostic schemes, lack of adjustment for potential confounders, and the inability to adjust for loss to follow-up. Such limitations may have given rise to the null effects observed in the meta-analysis discussed above. Other issues that have muddled the ecologic studies include differences in exposure definitions, such as variations in gestational periods of exposure between studies.

3.1.3.2. Studies based on birth cohorts: In our view, a potentially fruitful approach to either substantiate or refute the hypothesis that prenatal infection with influenza and other microbial exposures is related to risk of schizophrenia is to improve upon the study methodology. For this purpose, birth cohort, rather than ecologic studies, of prenatal infection and schizophrenia were conducted. These studies capitalized on methodologic advantages, including ascertainment of exposure to infections from assays of maternal antibody levels from archived serum specimens obtained from individual pregnancies, or in blood spots obtained from infants. Other studies made use of clinical diagnoses of infection documented by registry data during pregnancy.

3.1.3.2.1. Rubella: In the Rubella Birth Defects Evaluation Project (RBDEP), a birth cohort study conducted in New York City following the 1964 rubella pandemic, all mothers were documented with rubella exposure during pregnancy based on clinical diagnosis, and infection was serologically confirmed in offspring. Our group reported that exposure to rubella *in utero* conferred a greater than five-fold increased risk of non-affective psychosis (Brown et al., 2000a). Further follow-up of the cohort in mid-adulthood revealed that over 20% of rubella-exposed subjects were diagnosed with schizophrenia or a schizophrenia spectrum disorder (Brown et al., 2001). A substantially greater I.Q. decline, and greater premorbid neuromotor and behavioral anomalies, were also demonstrated in rubella-exposed schizophrenia cases, as compared to rubella-exposed controls. These latter findings bolstered the validity of the association and suggested that prenatal rubella might exert its effects on schizophrenia risk by altering the developmental trajectory during childhood and early adolescence. This finding is discussed in more detail in Section 4.2.

3.1.3.2.2 Influenza: In a follow-up of the Child Health and Development Study (CHDS), a population-based birth cohort in Alameda County, California born from 1959 to 1967, our group examined the relationship between prenatal influenza infection and schizophrenia in the offspring (Brown et al., 2004a). Maternal sera were drawn prospectively during pregnancy and stored frozen in a central repository. Offspring with schizophrenia were identified by databases from the Kaiser Permanente Medical Care Plan (KPMCP), a pre-paid health plan to which all mothers and offspring in the cohort belonged, and diagnoses in the Kaiser database were confirmed by a structured research interview. In addition to the methodologic advantages of birth cohort studies discussed above, it was possible to utilize dates of KPMCP membership to adjust for bias from loss to follow-up and to identify controls who represented the source population from which the cases were derived. A nested case-control design was used in this and in other serologic studies described below. This type of design entails selection of the cases and matched controls within a defined birth cohort. This approach obviated the costs of conducting serologic assays on the entire cohort. Maternal serum specimens corresponding to case and control offspring were assayed for antibody to influenza using standard methods.

Influenza during the first half of pregnancy was found to be associated with a three-fold increase in risk of schizophrenia in offspring (Brown et al., 2004a), and exposure during the first trimester was related to a seven-fold increased risk. Exposure to influenza during the second half of pregnancy was not related to schizophrenia. Hence, these findings suggest that early to mid-pregnancy may represent a period of susceptibility for the development of schizophrenia following influenza exposure.

It should be noted that in the meta-analysis of influenza described above (Selten et al., 2010), the three-fold increase in risk in our study, which narrowly missed statistical significance ($p = 0.052$), was not cited. It should also be underscored that the central conclusion of the meta-analysis, that there is insufficient evidence to support the influenza hypothesis of schizophrenia, is not incompatible with the conclusions of the seroepidemiologic study (Brown et al., 2004a). However, in our view, further ecologic studies do not represent a fruitful strategy to either confirm or refute this hypothesis, given their many limitations discussed above.

3.1.3.2.3. *Toxoplasma gondii* (*T. gondii*): *T. gondii*, an intracellular parasite, is a known cause of CNS congenital anomalies, which led to recommendations for pregnant mothers to minimize exposure to this pathogen. In addition to these overt manifestations, more subtle, delayed neuropsychiatric sequelae of *T. gondii* have been reported (Dukes et al., 1997; Remington and Klein, 2006). In the CHDS cohort, increased maternal levels of *T. gondii* IgG antibody (titers > 1:128) were associated with a greater than two-fold increased risk of schizophrenia among offspring (Brown et al., 2005b). This finding was essentially replicated in a Danish cohort in which *T. gondii* IgG was quantified in filter paper blood spots from infants up to 1 week old (Mortensen et al., 2007).

3.1.3.2.4. *Herpes simplex virus type 2* (HSV-2): HSV-2, a sexually transmitted disease acquired at the time of birth, is another known cause of congenital neuropsychiatric anomalies, including mental retardation, low-normal IQ, language deficits, and motor disability (Engman et al., 2008; Kropp et al., 2006). Prior epidemiologic studies of maternal HSV-2 and schizophrenia among offspring have yielded conflicting findings. In the Collaborative Perinatal Project (CPP), a multi-site population-based birth cohort study from 1959 to 1967, an association was demonstrated between maternal anti-HSV-2 IgG antibody levels and risk of psychotic disorders among offspring (Buka et al., 2001a). In a follow-up of this study with a larger sample, maternal seropositivity to HSV-2 was related to a 1.6-fold increase in risk of psychosis in offspring, and separate analysis of schizophrenic psychoses yielded a 1.8-fold increase in risk (Buka et al., 2008). These results were not replicated, however, in the CHDS birth cohort study (Brown et al., 2006); odds ratios were close to 1 for all analyses.

These discrepant findings may be explained by several factors. First, there was greater statistical power in the second of the CPP studies than in the CHDS study due to a larger proportion of African-Americans, given that HSV-2 is more prevalent among individuals of this ethnicity (Brown et al., 2006). A second issue is that different criteria for exposure were utilized in each of the two CPP studies. In the first, HSV-2 IgG antibody levels were used, but in the primary analysis of the second study, the exposure was based on HSV-2 seropositivity. In the CHDS cohort, the analyses were run under each of these two definitions of exposure, but neither definition yielded an association. A third difference between the studies concerns how loss to follow-up was addressed. In the CHDS, continuous follow-up of the cohort afforded the use of survival analytic methods, which mitigated bias from loss to follow-up; the CPP studies lacked population denominators over the period of follow-up. If cases whose mothers were exposed to HSV-2 had a greater

likelihood of remaining in the CPP cohort than controls without maternal HSV-2 exposure, bias may contribute to the finding.

3.1.3.2.5. Other prenatal infections in birth cohort studies: Birth cohort studies that related infections identified from obstetric and other medical records to schizophrenia risk have also been conducted. In the CHDS, periconceptional exposure to genital/reproductive infections was related to a five-fold increased risk of schizophrenia in offspring (Babulas et al., 2006). Exposure to maternal respiratory infection (Brown et al., 2000b), bacterial infection (Sorensen et al., 2009), and pyelonephritis (Clarke et al., 2009) have also been related to elevated risk of schizophrenia in offspring.

3.1.3.3. Proposed mechanisms

3.1.3.3.1. Cytokine-mediated effects: Investigators have addressed the question of potential mechanisms that mediate the associations between in utero exposure to infection and schizophrenia in offspring. One reason proposed for why several different infections, which vary in a number of respects, could give rise to schizophrenia is that they act through stimulation of the cytokine response (Gilmore and Jarskog, 1997; Patterson, 2009). This is plausible given that all of the infections investigated in studies of schizophrenia to date modify cytokine levels, and an excess of proinflammatory maternal cytokines has been associated with several neurodevelopmental disorders (Dammann and Leviton, 1997). Potential cytokine-induced mechanisms include stimulation of microglia and astroglia in the fetal brain to produce nitric oxide and excitatory amino acids, which are toxic to neurons (Patterson, 2009). Second, cytokines may disturb maturation of oligodendrocytes, contributing to white matter abnormalities, which have been found in postmortem studies of schizophrenia (Davis et al., 2003). Third, overactivation of cytokine-responsive pathways in the placenta or fetus may lead to developmental brain anomalies that could increase susceptibility to schizophrenia.

More recent data have supported important roles for cytokines and immune proteins in central nervous system (CNS) development (Deverman and Patterson, 2009). Cytokines have been implicated in neural induction, neurogenesis, and neuronal differentiation. Chemokines in particular appear to play important roles in neuronal migration, proliferation, and axon pathfinding. Cytokines also influence several functions of microglia, which are essential for CNS homeostasis and in immune surveillance following infection and injury. Cytokines also appear to regulate cell survival and facilitate synaptic refinement. Other immune proteins including those of the innate immune system, major histocompatibility (MHC) Class I molecules, and MHC Class I-binding immunoreceptors are important for the establishment, function, and modulation of synaptic connections (Boulanger, 2009). These findings provide a critical mechanistic link between normal and abnormal function of the immune system and of neurodevelopment, suggesting that disruptions of the immune response can alter several brain maturational events that have been previously posited as being involved in the pathogenesis of schizophrenia.

The CHDS and CPP birth cohort studies have supported a role for excess maternal cytokines in the development of schizophrenia among offspring. In the CHDS, maternal levels of the proinflammatory chemokine interleukin-8 (IL-8) in the second and early third trimester were increased two-fold among offspring who developed schizophrenia, compared to matched controls (Brown et al., 2004b). The plausibility of this finding is supported by the relationship between maternal serum IL-8 levels and histologic chorioamnionitis in term infants (Brown et al., 2004b), and the significant correlation between maternal and fetal levels of IL-8. IL-8 is known to play an important role in neutrophil attraction, and in discharge of lysosomal enzymes from neutrophils, producing oxygen free radicals which

may damage the fetal brain. In the CPP study, maternal levels of tumor necrosis factor- α (TNF- α), a proinflammatory cytokine, at the time of birth were elevated in pregnancies giving rise to psychotic disorders (Buka et al., 2001b). Intriguingly, TNF- α genetic polymorphisms have been associated with schizophrenia (Boin et al., 2001; Buka et al., 2001b).

In a DNA microarray study, Arion et al. (2007) examined gene expression changes in prefrontal cortex from 14 pairs of schizophrenia case and control brain samples. The authors observed an upregulation of genes related to immune function and the chaperone system. Among 19 fully annotated transcripts that were upregulated in schizophrenia, 10 have been associated with immune/chaperone functions. These included transcripts encoding 28 kDa heat shock protein, 70 kDa heat shock protein 1B, 70 kDa heat shock protein 1A, metallothionein 2A, interferon induced transmembrane protein 1, and others. Notably, all of these transcripts and their translated proteins exhibit increased expression in response to cellular stress and/or immune stimulation (Chung et al., 2003; Gossiau and Rensing, 2000; Xia et al., 2006). These genes were shown to cluster in a subsample of 5 schizophrenia patients in this study, suggesting that these molecules are co-regulated. The authors proposed that the immune/chaperone gene expression changes resulted from a long-term change of developmental origin in the transcriptome. This would suggest that immune activation in early life could be detected by a specific transcription profile of genes related to immune function.

3.1.3.3.2. Animal models of maternal immune activation (MIA): Basic neuroscience studies have further investigated the role of MIA in schizophrenia (for review, see Patterson, 2009). This has been accomplished by administration of three substances: polyinosinic:polycytidylic acid (poly I:C), a synthetic analogue of double stranded RNA, which mimics a viral infection, lipopolysaccharide (LPS), a bacterial cell wall endotoxin, and infection with human influenza virus.

Several studies have investigated the effect of maternal administration of poly I:C on brain and behavioral deficits in offspring. Poly I:C exerts its effects through the toll-like receptor (TLR)3. Abnormalities include deficits in pre-pulse inhibition (PPI), latent inhibition, social interaction, working memory, novel object exploration, excessive amphetamine-induced locomotion, and enhanced reversal learning (Meyer et al., 2005, 2006; Ozawa et al., 2006; Shi et al., 2003, 2009b; Smith et al., 2007; Wolff and Bilkey, 2008; Zuckerman et al., 2003). Some of these findings, such as amphetamine-induced locomotion, aspects of working memory dysfunction, and disrupted latent inhibition suggest dysfunction of dopaminergic activity (Ozawa et al., 2006), and increased striatal dopamine release in response to amphetamine has also been observed (Zuckerman and Weiner, 2005). Moreover, reduced dopamine D1 and D2 receptors in the prefrontal cortex and increased tyrosine hydroxylase in striatum have been reported (Meyer et al., 2008d). Some evidence suggests that gamma-aminobutyric-acid (GABA)-ergic function may also be impaired, in that adult offspring of poly I:C-treated mothers had elevated GABA-A receptor α -2 immunoreactivity (Nyffeler et al., 2006). Glutamatergic dysfunction is suggested by reduced N-methyl-D-aspartate (NMDA) receptor expression in the hippocampus (Meyer et al., 2008c) and increased locomotion after administration of the NMDA antagonist MK-801 (Zuckerman et al., 2003; Zuckerman and Weiner, 2005). Other findings reminiscent of clinical observations in schizophrenia include ventricular enlargement (Piontkevitch et al., 2007) and decreased numbers of reelin- and parvalbumin positive cells in the prefrontal cortex (Meyer et al., 2008b). Meyer and Feldon (2010), in a recent review, summarize how the findings on MIA relate to hypothesized relationships between dopaminergic hyperactivity in the nucleus accumbens, diminished inhibitory control from the prefrontal cortex and ventral

hippocampus, and disrupted activation of prefrontal excitatory glutamatergic inputs on inhibitory GABAergic neurons in the nucleus accumbens.

The findings from MIA animal models also appear consistent with the time course of schizophrenia symptomatology. Schizophrenia is rare during childhood, but rather emerges during adolescence and early adulthood. This has raised the apparent paradox of how the neural substrates that ultimately give rise to the overt psychotic symptoms of the disorder could originate as early as the fetal period but remain quiescent throughout all of childhood and part of adolescence (see Section 4.2). Animal models of MIA may have already helped to resolve this paradox, in that in several of these studies, the brain and behavioral abnormalities described above were not found during the juvenile period, but instead emerged post-pubertally, analogous to the age of onset of schizophrenia (Meyer et al., 2006; Ozawa et al., 2006; Zuckerman et al., 2003; Zuckerman and Weiner, 2005).

In further support of the MIA models of schizophrenia, some of these abnormalities, including disrupted latent inhibition, were reversible by antipsychotic medication (Ozawa et al., 2006; Zuckerman et al., 2003). Intriguingly, antipsychotic treatment in immature offspring prevented the emergence of several brain and behavioral abnormalities. Patterson and others have pointed out in this context that antipsychotics have been demonstrated to modify cytokine gene expression (Drzyzga et al., 2006; Patterson, 2009; Pollmacher et al., 2000).

Maternal exposure to LPS causes a number of offspring phenotypes that mirror those found in the poly I:C model and that are relevant to schizophrenia. Histologic findings include decreased myelin basic protein (Cai et al., 2000) and myelin (Paintlia et al., 2004), and increased dopamine in the nucleus accumbens (Romero et al., 2007). Neurophysiologic and behavioral findings include PPI deficits which are corrected by antipsychotic medications (Borrell et al., 2002; Romero et al., 2007), increased amphetamine-induced locomotion (Fortier et al., 2004), and social interaction deficits.

In a further test of mechanisms by which cytokines lead to these developmental brain deficits, Smith et al. (2007) found that maternal injection of IL-6 during mid-pregnancy caused deficits of prepulse inhibition and latent inhibition in adult offspring. Administration of anti-IL-6 antibody prevented these effects and they were also not observed in an IL-6 genetic knock out mouse. Although IL-6 appears to play an essential role, these findings do not rule out contributions of other cytokines. As an example, direct treatment of embryonic rat cortical cultures with IL-1- β and TNF- α caused dose-dependent decreases in microtubule associated protein-2 (MAP-2) immunoreactivity (Marx et al., 2001), suggesting that cytokines decrease survival of cortical neurons during gestation.

Studies of MIA have also investigated their effects on the fetal environment. Elevations of several pro-inflammatory cytokines have been observed in the placenta and amniotic fluid of offspring exposed to LPS (Boin et al., 2001; Mino et al., 2000) and poly I:C in utero (Patterson, 2009).

3.1.3.3.3. Individual effects of infections: It is also possible that prenatal infections act by unique mechanisms to influence risk of schizophrenia. This is supported by the fact that infections associated previously with schizophrenia differ in several respects; these include duration of symptoms, antigenicity and antibody response, and gestational specificity to known congenital outcomes. Influenza is not believed to cross the placenta, remaining confined to the respiratory tract. It has been proposed that influenza elicits IgG antibodies, which cross-react with fetal brain antigens by molecular mimicry (Wright et al., 1999).

Influenza could also affect brain development by non-specific effects, such as hyperthermia, fetal hypoxia, and over-the-counter medications, such as aspirin.

In animal models, intranasal maternal infusion of influenza during mid-gestation in pregnant mice caused specific histologic anomalies in the hippocampus and cortex of neonatal offspring, including changes in expression of SNAP-25, a presynaptic marker, neuronal nitric oxide synthase (nNOS) (Fatemi et al., 2000, 1999), and reduced reelin-positive Cajal-Retzius cells in several cortical layers and the hippocampus, but without corresponding alterations in calretinin and nNOS, indicating abnormal reelin production rather than greater cell death (Fatemi et al., 1999). Mice neonatally infected with influenza also displayed diminished cortical and hippocampal area and an increase in cortical pyramidal cell density and more tightly packed pyramidal cells (Fatemi et al., 2002).

In utero exposure to influenza also results in behavioral, neurophysiologic, and neurochemical abnormalities in rodent offspring, including deficits in social interaction, prepulse inhibition to acoustic startle, open field activity and exploration of novel objects (Shi et al., 2003). The PPI deficits were reversed by the antipsychotics clozapine and chlorpromazine. Maternal influenza also results in increased sensitivity to treatment with NMDA-receptor antagonists (Shi et al., 2003). Studies of prenatal influenza-exposed offspring exhibited alterations in gene transcription (Fatemi et al., 2005; Winter et al., 2008).

In a recently published primate model, influenza infection of pregnant rhesus macaques during the latter half of pregnancy caused reduced intracranial and cortical gray matter volume, including of the left cingulate and the left parietal lobe, following correction for intracranial volume (Short et al., 2010). A trend for decreased total white matter, particularly of the cerebellum, was also observed. Moreover, IgG antibody levels to influenza were correlated in that study with increased ventricular size. These findings are of greater relevance to humans for four reasons: first, infection was possible with a human-derived H3N2 strain; second, rhesus macaques have a hemochorial placenta, as do humans, enabling increased communication between maternal and fetal physiologic factors; third, macaques give birth to one offspring at a time; fourth, brain development is more advanced in primates than in rodents (Short et al., 2010). In spite of these very intriguing findings, the gestational timing of infection in that study was probably later than in most rodent models of infection and MIA and not consistent with the timing of influenza exposure that gave rise to schizophrenia in the one epidemiologic study to investigate this question with maternal biomarkers of exposure (Brown et al., 2004a) (see Section 3.1.3.2.2). Hence, it will be important to examine the effect of influenza infection during early and mid-pregnancy on these and other phenotypic outcomes.

It is also worth noting that many of the brain and behavioral anomalies demonstrated in the poly I:C model were similar to those evoked by the maternal influenza model. This suggests that the maternal immune response may be one of the most critical factors mediating the potential effects of maternal influenza exposure on schizophrenia in the offspring, consistent with the fact that influenza is not known to cross the placenta and to enter the fetal circulation.

With regard to *T. gondii*, it is unlikely that active primary infection is sufficient to explain its association with schizophrenia, since maternal or neonatal anti-*T. gondii* IgM antibody, which is indicative of recently acquired infection, was not observed in the two previous epidemiologic studies of this pathogen and schizophrenia reviewed above (Brown et al., 2005b; Mortensen et al., 2007). *T. gondii* can also be reactivated in a host who was previously exposed, resulting in an inflammatory fetal brain response, which could possibly be accompanied by increased maternal anti-*T. gondii* IgG antibodies. Elevated anti-*T. gondii*

IgG antibodies, which may persist for many years following infection, are capable of crossing the placenta, and previous studies of autoimmune disorders suggest that elevated total IgG antibody is teratogenic (Nadler et al., 1995). Maternal genital/reproductive infections can disrupt fetal neurodevelopment by direct fetal invasion, following ascension from the perineum, vagina, or cervix (Babulas et al., 2006; Remington et al., 2006).

3.1.3.3.4. Other mechanisms: Although the parsimony and plausibility of an elevation of maternal cytokines is an attractive mechanism for the associations between prenatal infection and schizophrenia, there are a number of additional potential pathogenic mechanisms. These include, among others, febrile responses, malnutrition (see Section 3.1.4), and fetal/neonatal hypoxia (see Section 3.1.6). Fever, which is associated with the cytokine increase, may also have teratogenic effects, given that hyperthermia is a known cause of neural tube defects, central blindness, deafness, hypotonia, seizures, micrencephaly, and learning and behavioral abnormalities (Edwards, 2006). Moreover, febrile individuals may suffer from dehydration and other physiologic impairments that could disrupt optimal uteroplacental function. Both chronic and acute infections are associated with malnutrition due to the reduction of nutrient intake and altered utilization of nutrients that accompany them (Wintergerst et al., 2007), and infection and inflammation can increase the sequestration of iron, resulting in iron deficiency anemia (Collins, 2008), which has been associated with schizophrenia in two studies (see Section 3.1.4.2.2). Furthermore, malnutrition also acts as an antecedent to infection, given that macro- and micronutrient deficits can suppress physiologic immune activation by altering innate T-cell-mediated immune and adaptive antibody responses, thereby increasing the susceptibility to infection (Wintergerst et al., 2007). Chorioamnionitis induced by a variety of maternal infections can sensitize the fetal brain to increased damage by hypoxic events, a process which is mediated in part by the maternal and fetal inflammatory response (Ugwumadu, 2006).

3.1.4. Nutrition—The season of birth findings in schizophrenia, discussed above in relation to infection, also led investigators to hypothesize that prenatal nutritional factors might be involved in schizophrenia (Tramer, 1929), given that a number of nutrients may vary over the course of the year, with deficiencies related to changes in intake or sunlight, in the case of vitamin D. A second reason for considering prenatal nutrition in the etiology of schizophrenia is the fact that a number of known neuropsychiatric disorders are related to nutritional deprivation, or are improved upon vitamin and mineral supplementation during pregnancy. This includes neural tube defects, which are prevented by supplementation with folic acid, and iodine deficiency, a known cause of cretinism (Brown et al., 1996). A third reason for a focus on nutrition in pregnancy is the high prevalence of deficiency states throughout the world. Maternal and child malnutrition is associated with high mortality and morbidity (Black et al., 2008), particularly in the developing world; however, maternal deficiencies of many micronutrients have high prevalence in both developed and developing countries (Ames, 2001).

Below is a review of studies of prenatal nutrition and schizophrenia, including translational studies of these exposures. The findings presented here, and results of additional studies, are summarized in Table 1.

3.1.4.1. Famine studies: The first evidence supporting a role of prenatal malnutrition in schizophrenia derives from studies on in utero exposure to famine. In the Dutch Hunger Winter of 1944–1945, which was precipitated by a Nazi blockade of the Netherlands and other factors, there was a severe decline in caloric intake in the western region of Holland. In this part of the country, the daily food ration fell to less than 500 calories (McClellan et al., 2006). As expected, this tragic event had marked effects on the health of the population, with a doubling of mortality and a halving of fertility. Investigators have made use of data

collected from the Dutch Hunger Winter in order to investigate the relationship between famine and health outcomes, including human development and neuropsychiatric function (Stein et al., 1975; Susser et al., 1996). A research study of prenatal famine in relation to risk of schizophrenia was made possible by excellent documentation of food rations to the population, the circumscribed nature of the famine, and the availability of national psychiatric registries with diagnoses of schizophrenia (Hoek et al., 1998; Susser et al., 1996). The authors found that the occurrence of severe famine during the time of conception or early pregnancy was related to a two-fold increase in risk of schizophrenia in the offspring. The plausibility of the findings was supported by the co-occurrence of a peak in anomalies of the central nervous system, including neural tube defects, during this same period of pregnancy in this cohort.

These results have since been replicated in two subsequent studies which investigated schizophrenia following the Chinese famine of 1959–1961, which was part of Mao Zedong's Great Leap Forward (St Clair et al., 2005; Xu et al., 2009). Both of these studies were conducted in two severely affected regions, Wuhu (Anhui province) and the Liuzhou region of southern China that used a similar design as the Wuhu study. In these studies, the risk of schizophrenia peaked for those annual birth cohorts in which the birth rate declined (Xu et al., 2009). What was of particular importance is that the two regions differed markedly by ethnicity, customs, and the contextual experience of the famine. Hence, concordant results between three very different cohorts provides strong evidence that prenatal famine is related to risk of schizophrenia.

These studies, however, had a significant limitation. All were ecologic studies, based on the timing of famine in a population. Therefore, it is unclear whether nutritional deprivation or many factors that accompany famine, including epidemics of infection (see Section 3.1.3), severe stress (see Section 3.1.7.3), ingestion of toxic substances, or a combination of these factors were responsible for the observed associations. As reviewed elsewhere in this article, each of these exposures have been associated previously with risk of schizophrenia. Even within the category of nutrient deficiency, it is unclear whether protein-calorie deprivation, a host of micronutrient deficits, or interactions between several of them, accounted for the findings. Moreover, famine is an experience that does not occur in most populations in which schizophrenia is measured, and hence it is an open question as to whether these findings are generalizable to non-famine-exposed populations. Hence, it is essential first to better understand how macronutrient deficiency during gestation might result in phenotypes among offspring that are concordant with the neurobiology of this disorder. Second, it is necessary to further investigate specific prenatal micronutrient deficiencies which would have clearly accompanied these famines.

3.1.4.1.1. Animal models of prenatal protein deprivation (PPD): Animal models of PPD have helped to validate the epidemiologic findings on prenatal famine in relation to the risk of schizophrenia. In these studies, pregnant animals are placed on protein-deficient diets during pregnancy, and offspring from these pregnancies are compared to offspring from pregnant mice on a non-protein deprived diet. These studies have demonstrated that prenatal PPD alters morphology and dendritic architecture of the frontal cortex (Bronzino et al., 1997; Cintra et al., 1990; Debassio et al., 1994; Diaz-Cintra et al., 1991, 1994; Lister et al., 2005; Morgane et al., 2002), diminishes sensorimotor gating (Palmer et al., 2004), and increases sensitivity to acutely administered direct and indirect dopamine receptor antagonists (Brioni et al., 1986; Palmer et al., 2008; Shultz et al., 1999) and NMDA receptor antagonists (Tonkiss et al., 1998). Moreover, offspring that were protein deprived during gestation exhibit diminished working memory (Ranade et al., 2008) and reversal learning. Some of these anomalies, such as sensorimotor gating and increased sensitivity to dopaminergic and glutamatergic compounds are not present until after puberty (Palmer et

al., 2008, 2004), consistent with the developmental time course of the symptoms of schizophrenia. It should be noted that, in one study, the sensorimotor gating deficit and increased sensitivity to dopaminergic compounds were present in female but not male offspring (Palmer et al., 2004).

3.1.4.2. Micronutrient deficiency

3.1.4.2.1. Folate/homocysteine: The concordance in the schizophrenia and neural tube defect outcomes following periconceptional and early gestational exposure to famine suggested that prenatal folate deficiency might be a potential etiologic factor. Folate is a single-carbon donor which plays several roles in cellular physiology, genetic structure, and epigenetic pathways, including nucleotide synthesis, DNA repair, and methylation.

Homocysteine is an amino acid that is a part of the same metabolic cycle including folate and several other molecules. Low serum folate levels result in elevated homocysteine levels, since folate donates a methyl group to homocysteine, allowing for conversion to methionine, a reaction catalyzed by methionine synthase (Graham, 1997). Vitamin B12 acts as a co-factor in this pathway. Serum homocysteine therefore represents a marker of folate levels, but homocysteine and its derivatives may play other roles that could potentially alter neurodevelopment, including antagonism of the N-methyl-D-aspartate receptor (NMDAR), which has been implicated in schizophrenia (Goff and Coyle, 2001). Perinatal administration of PCP, an NMDA receptor antagonist, impairs locomotion, working memory, and pre-pulse inhibition (Baschat, 2004), and reduces synaptophysin (Wang et al., 2004) abnormalities that have been found in schizophrenia (Egret, 2003; Self et al., 1992). Perinatal exposure to MK-801, another NMDA receptor antagonist, caused reduced volume of the subiculum and neuronal number in the CA1 region of the hippocampus (Olney, 2004), disturbances of which have also been demonstrated in schizophrenia. Elevated homocysteine also alters fetal synapse development, plasticity, and neuronal migration (Picker and Coyle, 2005). Moreover, increased homocysteine leads to several pathologic alterations in the placenta, which can compromise delivery of oxygen to the fetus (Dalman et al., 2001b); as noted in Section 3.1.6, many studies have implicated fetal hypoxia in schizophrenia (Cannon et al., 2002a). Finally, elevated homocysteine has been related to several obstetric complications, including pre-eclampsia, recurrent miscarriage, abruptio placentae, premature delivery, and low birthweight, complications previously associated with schizophrenia in offspring (Cannon et al., 2002a; Graham, 1997; Jones et al., 1998) (see Section 3.1.6).

In the CHDS birth cohort, elevated third trimester serum homocysteine levels were associated with an increased risk of schizophrenia (Brown et al., 2007); however, no effect was observed for the first trimester, the period during which low folate was hypothesized based on the famine studies.

3.1.4.2.2. Iron: Prenatal iron deficiency is a plausible risk factor for schizophrenia, given that this nutrient plays a key role in myelination (Connor and Menzies, 1996) and dopaminergic neurotransmission (Ben-Schachar et al., 1986). Oligodendrocytes require iron for proper production of myelin. Restriction of iron during gestation and lactation to pregnant mice led to significant differences in myelin fatty acid composition, which persisted despite postnatal iron repletion in the diet of the offspring (Kwik-Urbe et al., 2000). Iron deficiency during gestation also led to less total myelin protein and decreased cholesterol, phospholipids, and galactolipids in myelin (Ortiz et al., 2004). Myelin and oligodendrocyte deficits have been demonstrated in postmortem studies of schizophrenia (Davis et al., 2003; Flynn et al., 2003; Hakak et al., 2001). More recent and direct evidence for iron abnormalities in schizophrenia has been demonstrated by transferrin and ferritin changes in a proteomics study of postmortem brains (English et al., 2009).

Iron depletion during pregnancy also caused an increased ratio of dopamine metabolites [3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)] to dopamine in the caudate of offspring; these alterations persisted in females following postnatal iron repletion (Kwik-Urbe et al., 2000). Dopaminergic dysfunction is one of the hallmark features of schizophrenia (Akil et al., 1999; Laruelle et al., 1996; Meyer-Lindenberg et al., 2002). Moreover, maternal iron deficiency causes anemia, which can lead to fetal hypoxia, a complication previously implicated as a risk factor for schizophrenia (Cannon et al., 2000; Dalman et al., 2001a; Zornberg et al., 2000).

Additional evidence suggests that low maternal iron may serve as a point of convergence of other putative schizophrenia risk factors, including maternal stress (see Section 3.1.7.3), infection (see Section 3.1.3), and inflammation (see Section 3.1.3.3.1). Maternal stress during pregnancy has been demonstrated in animal models to cause iron deficiency anemia by affecting the transfer and utilization of this micronutrient, which leads in turn to diminished cytolytic activity of natural killer (NK) cells thereby increasing the susceptibility to maternal infection (Coe et al., 2007). Lower birth weight and consequent catch-up postnatal growth during early life increases demands on iron and contributes further to the effect of iron deficiency on NK functioning (Coe et al., 2007).

In the CHDS cohort, we demonstrated that a maternal hemoglobin concentration of 10 g/dL or less was associated with a nearly four-fold increased risk of schizophrenia, following adjustment for maternal education and ethnicity (Insel et al., 2008). The effect was present for exposure during the second trimester, as well as the third trimester. This finding has been replicated in a large national cohort of Danish births, in which a hemoglobin level less than 11 g/dL was associated with an adjusted relative risk of nearly 1.7 (Sorensen et al., in press). It was not possible in the latter study, however, to examine the effect of hemoglobin less than 10 g/dL, nor to examine dose-response effects. Since iron is required for hemoglobin synthesis, this suggests that iron may be playing an etiologic role; although as noted in the preceding paragraph, low maternal hemoglobin may also predispose to fetal hypoxia, which could have mediated the observed effect.

3.1.4.2.3. Vitamin D: Vitamin D was hypothesized as a risk factor for schizophrenia based on several lines of evidence (McGrath, 1999). First, it has been invoked to explain the winter/spring excess of schizophrenia births discussed above (see Section 2.2.2) given that reduced sunlight lowers vitamin D levels. Second, individuals with darker skin, who have lower levels of vitamin D, were shown in previous studies to have an increased risk of schizophrenia (Bresnahan et al., 2007; Cantor-Graae and Selten, 2005) (Section 2.1.4).

Third, animal models suggest that prenatal vitamin D deficiency is associated with structural and functional brain deficits that have been observed previously in patients with schizophrenia (McGrath, 1999). These include behavioral and neurophysiologic deficits including increased novelty-enhanced hyperlocomotion (Burne et al., 2004), sensitivity to psychotomimetic drugs including the non-competitive NMDA-R antagonist MK-801 (Kesby et al., 2006), the D2 receptor antagonist haloperidol, and amphetamine; and disrupted latent inhibition (Becker et al., 2005), which reflects selective attention to relevant aspects of the environment (Weiner, 2003). Additional observations include gross structural brain abnormalities, including larger lateral ventricles and a thinner neocortex (Eyles et al., 2003), and a reduction in the expression of catechol-O-methyl transferase (COMT), a key dopamine metabolic enzyme in the cortex (Kesby et al., 2009), reduced brain levels of neurotrophins and neurotrophin receptors (Eyles et al., 2003), diminished brain apoptotic activity (Ko et al., 2004), and impaired neurogenesis (Cui et al., 2007).

Presently, two epidemiologic studies have been conducted to test the vitamin D deficiency hypothesis in schizophrenia. The first, based on the birth cohort of the Providence site of the CPP, evaluated vitamin D levels in a modest number of schizophrenia and control offspring whose mothers had third trimester serum samples available (McGrath et al., 2003). Although there was no significant difference between cases and controls, the authors observed a trend for diminished maternal vitamin D levels in case offspring among the African-American subgroup ($p = 0.08$). The negative findings of this study may be a result of low statistical power due to the modest sample size. In a more recent study of neonatal vitamin D assayed from filter paper blood spots collected in Denmark, an increased risk of schizophrenia was observed following exposure to vitamin D levels in the lowest three quintiles and highest quintile, with the lowest risk in the fourth highest quintile (McGrath et al., 2010). This curvilinear effect suggests that there may be an optimal “window” of vitamin D in newborns with regard to prevention of schizophrenia.

3.1.4.2.4. Elevated body mass index (BMI): In the CHDS birth cohort, high compared with average maternal pre-pregnant BMI, prospectively documented, was associated with a nearly three-fold, significantly increased risk for SSD in adult offspring (Schaefer et al., 2000). Although this finding appears to be inconsistent with the famine findings, it may reflect an increase in certain other putative schizophrenia risk factors associated with obesity. For example, overweight individuals may be less attentive to adequate micronutrient intake, suffer from diabetes, or be more likely to experience obstetric complications, each of which have been associated with schizophrenia as discussed in this review.

3.1.5. Advanced paternal age—Advanced paternal age at the time of birth of the offspring is one of the oldest and best replicated findings in epidemiologic studies of schizophrenia. This topic has been extensively reviewed in a previous publication (Miller et al., 2010); hence, the reader is referred to that publication for a summary table. The first evidence supporting this association was published over 50 years ago (Johanson, 1958). In spite of several replications, it was unclear whether paternal age, maternal age, or both, were responsible until Hare and Moran (1979) isolated the effect to older fathers. These authors postulated that the findings were accounted for by a constitutional parental trait leading to delayed marriage. No studies of this putative risk factor were conducted for over 20 years, when Malaspina et al. (2001), in the Jerusalem Perinatal Study (JPS), a large birth cohort from the 1960s and 1970s, demonstrated a monotonic association between advancing paternal age and risk of schizophrenia in the offspring. For fathers aged 45–49, the risk of schizophrenia was increased two-fold, and for fathers over age 50, there was a three-fold effect, compared to fathers less than 25 years old. Subsequent studies, conducted in the USA (Brown et al., 2002; Torrey et al., 2009), Europe (Byrne et al., 2003; Dalman and Allebeck, 2002; Ekeus et al., 2006; El-Saadi et al., 2004; Laursen et al., 2007; Lopez-Castroman et al., 2010; Sipos et al., 2004; Zammit et al., 2003), Australia (El-Saadi et al., 2004), and Japan (Tsuchiya et al., 2005) were for the most part positive, with monotonic effects, though effect sizes differed somewhat between studies (Miller et al., 2010). In addition to the use of birth cohorts, the more modern studies differed in that they were capable of controlling for potential confounding factors, and diagnoses that were based on more standardized criteria for schizophrenia. With regard to adjustment for confounding, the findings persisted controlling for family history (though see discussion below), maternal age, parental education, social class, birth order, birth weight, and birth complications.

In the paper from the JPS (Malaspina et al., 2001), the hypothesis was put forward that *de novo* mutations might be responsible for these effects. Unlike the germ cells of the female, the male spermatogonial stem cells undergo constant replication, from 150 replications by age 20 to 840 by age 50 (Kuhnert and Nieschlag, 2004). The cumulative effect of these

divisions is an increase in point mutations, resulting from copy and transcription errors, which may increase with aging due to diminished DNA repair mechanisms (Crow, 2000). *De novo* mutations involving single base pair changes in select genes increase sharply with male age and have been shown to cause rare autosomal dominant birth defects, including achondroplastic dwarfism (Orioli et al., 1995), Apert's syndrome, and Crouzon's syndrome (Kuhnert and Nieschlag, 2004). Interestingly, however, no increase of *de novo* structural chromosomal anomalies has been found in newborns from older fathers (Hook et al., 1984).

A second potential mechanism might involve aberrant epigenetic regulation (Perrin et al., 2007). Epigenetic effects are heritable changes in gene expression that result not from changes in DNA sequence, but as a result of DNA methylation, demethylation, and histone modifications that alter chromatin structure (see Section 5.2.3). The result of such changes is either the silencing of genes by preventing transcription or activation of genes by allowing transcription. The relevant processes by which epigenetic changes in the paternal germ cell line can be transmitted to the fetus is a process known as imprinting. Some genes known to be imprinted play an important role in placental and fetal growth including development of the central nervous system. During gametogenesis, genes are differentially "marked" following "erasure" of methylation patterns of the previous generation and further changes in chromatin are established (Ferguson-Smith and Surani, 2001; Jiang et al., 2004). This process results in differential silencing or activation of the paternal or maternal allele. Errors may occur either in the process of imprinting or erasure of methylated genes. Imprinting errors can cause partial or complete biallelic expression of a gene, and imprinting errors have been associated with neurodevelopmental disorders (Cruz-Correa et al., 2004; Walter and Paulsen, 2003). In order to substantiate whether an effect of advanced paternal age is mediated by *de novo* mutations or disturbances in epigenetic regulation, studies are presently investigating whether advanced paternal age is related to new mutations and deviant methylation patterns in offspring with schizophrenia.

These findings are bolstered by corollary evidence that advanced paternal age is associated with neurocognitive and social deficits. In a large sample of offspring from the JPS, not selected for having schizophrenia, increased maternal and paternal age were associated with diminished intelligence; advanced paternal age was specifically related to performance intelligence, with a sparing of verbal intelligence, while advanced maternal age was associated with lower verbal and performance intelligence (Malaspina et al., 2005). In a comparably designed study from the CPP birth cohort, advanced paternal age was related to impaired performance on most neurocognitive tests in offspring, while advanced maternal age was associated with better performance on several domains of intelligence (Saha et al., 2009), in contrast to the study from the JPS. In a commentary on the latter study, Cannon (2009) suggests that social advantage (i.e. economic security, increased education) may compensate for the biological risks of delaying motherhood, and that the contrasting paternal and maternal age effects could be related to differences in parental interactions with their children.

Animal models have investigated the effects of advanced paternal age on offspring behavior, cognition, and neuromorphology. Decreased spontaneous activity and poorer learning capacity were documented in offspring of older males (Auroux, 1983). In more recent animal studies, the offspring of older males were shown to have impaired learning and diminished exploration (Bradley-Moore et al., 2002), as well as less social behaviors (Smith et al., 2009), and disruptions in cortical growth. More recently, advanced paternal age was shown to cause increased anxiety-related behaviors in female offspring, and curiously, thinner cortices at birth, but increased total cortical volume in male adults (Foldi et al., 2010). The latter two findings may re-capitulate features of autism, which has also been associated with advanced paternal age (Reichenberg et al., 2006).

Although there seems to be little doubt that advanced paternal age is associated with schizophrenia in offspring, several challenges remain with regard to fully confirming that this is due to a biological phenomenon. While the association in previous studies clearly persisted following adjustment for family history, and there is evidence for increased paternal age in sporadic but not familial cases of schizophrenia, Pulver et al. (2004) found no association between paternal age at birth and risk of schizophrenia or psychotic disorders in paternal relatives, nor were any differences observed between paternal age in sporadic versus familial probands. Although, as noted above, animal and human studies suggest that advanced paternal age has an impact on neurocognition and social behavior, identifying the specific biological mechanisms, such as de novo mutations and epigenetic aberrations, will prove to be challenging, though not insurmountable, given the likelihood that many genes may harbor such defects, and the difficulty in disentangling factors that may be causal from those that are consequences of schizophrenia.

3.1.6. Obstetric complications—Along with advanced paternal age (see next section), non-specific complications of pregnancy and delivery, generally referred to as “obstetric complications (OCs),” rank among the first epidemiologic findings shown to contribute to susceptibility for schizophrenia. Both case–control and population-based research designs have been utilized. There are three published meta-analytic studies of OC's and schizophrenia. The reader is referred to these publications for summary tables.

The meta-analysis by Cannon et al. (2002a) was limited to population-based studies. Significant findings were reported in regard to three OC's: complications of pregnancy (bleeding, preeclampsia, diabetes, rhesus incompatibility), abnormal fetal growth and development (low birth weight, congenital malformations, small head circumference), and complications of delivery (asphyxia, uterine atony, and emergency Cesarean section). Effect sizes for most of these complications were generally below two, though greater than three-fold effects were reported for diabetes, placental abruption, low birthweight, and emergency C-section.

An earlier meta-analysis, by Geddes and Lawrie (1995), was based on all publications that provided data on schizophrenia cases and a control group of subjects without schizophrenia, and that reported the methodology for diagnosis of schizophrenia and of measurement of the exposures. The authors found a pooled odds ratio of 2.0 (95% CI 1.6–2.4) for the effect of the OC's on schizophrenia.

Geddes et al. (1999) conducted an additional meta-analysis, of individual patient data from 12 case–control studies, based on use of the Lewis-Murray Scale for Obstetric Complications. Significant associations were reported for premature rupture of membranes, prematurity, and resuscitation or incubator use, while low birthweight and forceps delivery were of borderline significance.

Several limitations of these studies have been discussed by the authors of these meta-analyses. Ascertainment bias and confounding have the potential to cause spurious results; case–control studies are more susceptible to such artifacts. Exposures including low birthweight are unlikely to play a causal role, but may rather be proxies of particular prenatal factors, or may reflect prematurity. This limitation could be addressed by adjusting for gestational age, which was not done in most studies. Interactions between OC's and other clinical or demographic factors have not been performed; however, in a meta-analysis, OC's and schizophrenia were significantly associated only in subjects younger than age 25 (Verdoux et al., 1997). As noted by Geddes and Lawrie (1995), there was significant heterogeneity between the case–control and cohort studies. Finally, several studies

quantified OC's by maternal recall of the event, including after the diagnosis of schizophrenia in the offspring was already made, which may have resulted in recall bias.

The heterogeneity of these OC's renders interpretations regarding pathogenic mechanisms difficult. One mechanism that is frequently invoked is fetal or perinatal hypoxia, given known associations between several of these OC's and the occurrence of hypoxia during pregnancy. It is unclear, however, whether hypoxia represents a common mechanism to explain the effects of these diverse OC's, or the extent to which other influences acting earlier in pregnancy may explain the observed relationships, or act as antecedent factors. Other mechanisms that have been considered are mechanical trauma during delivery, which may be caused by the OC's or be a result of their treatment, and risk factors that predispose to, or result from, prematurity.

Several preclinical models have tested the neurobiological effects of insults that are caused by, or related to, a number of the OC's reported in the epidemiologic studies of schizophrenia (Meyer and Feldon, 2010). One model that has been used in order to attempt to re-capitulate respiratory alterations and very low grade CNS hypoxia during the first 24 h is Cesarean-section (C-section) (El-Khodor and Boksa, 2001), which, as noted above has been associated previously with schizophrenia (Cannon et al., 2002a). Offspring of dams born via C-section evidenced increased behavioral sensitivity to acute amphetamine (El-Khodor and Boksa, 1998; Vaillancourt and Boksa, 1998) and stress (El-Khodor and Boksa, 2000), and sensorimotor deficits were observed in guinea pigs from pregnancies with experimental C-section (Vaillancourt and Boksa, 2000). Other offspring outcomes of this model relevant to schizophrenia included a more sustained dopamine response in the nucleus accumbens (Brake et al., 1997) and diminished dopamine in the prefrontal cortex following stress (Brake et al., 2000). In another paradigm, involving exposure of pups to temporary intra-uterine anoxia during C-section birth, greater stress-induced sensitization to amphetamine (Brake et al., 1997), and to repeated stress exposure (El-Khodor and Boksa, 2000) were observed. In a subsequent study, these outcomes were shown to occur in early adulthood but not in the pre-pubertal period (Juarez et al., 2003). Other findings from this model included increased responses to dopamine-stimulating agents in the nucleus accumbens (Wakuda et al., 2008) and diminished stress-induced prefrontal cortical dopamine release (Brake et al., 2000). In a third model, involving restriction of utero-placental blood flow, enlarged ventricles, decreased hippocampal volumes (Mallard et al., 1999), decreased neurotrophic factors in the hippocampus (Dieni and Rees, 2003), and impaired sensorimotor gating (Rehn et al., 2004) were observed.

3.1.7. Other prenatal exposures

3.1.7.1. Lead: Lead has long been known to have neurotoxic effects, with exposure during childhood associated with several neurocognitive and behavioral deficits. In the schizophrenia follow-up study of the CHDS birth cohort, Opler et al. (2004), using maternal second trimester sera drawn from pregnancies that gave rise to cases of schizophrenia, and maternal sera of matched controls, demonstrated an approximately two-fold effect of elevated levels of delta-aminolevulinic acid (d-ALA), a proxy biomarker of lead exposure, on risk of schizophrenia. A similar finding was observed when the CHDS subjects were combined with subjects from the CPP birth cohort (Opler et al., 2004). These findings suggest that the neurodevelopmental disruption from prenatal exposure to lead could increase susceptibility to schizophrenia. The results persisted after adjustment for several potential confounders, including race and socioeconomic status. The findings, however, do not rule out potential effects of continued exposure to lead in infancy and childhood, since one would expect a correlation between environmental levels of lead during the prenatal period and those epochs of life.

Lead could modify risk of schizophrenia through several mechanisms. First, direct interactions could involve effects on growth and differentiation of the CNS, given that lead can alter neural adhesion molecules (Prozialeck et al., 2002) and synaptic function, including NMDA receptor expression (Toscano et al., 2002). Indirect mechanisms have also been postulated (Opler et al., 2004), including renal damage (Loghman-Adham, 1997), effects on transthyretin secretion in the choroid plexus (Zheng et al., 1999), and interactions with nutrient absorption. It is also possible, as noted previously (Opler et al., 2004), that d-ALA could increase schizophrenia risk through neurotoxic effects on GABA neurotransmission (Percy et al., 1981).

3.1.7.2. Rhesus (Rh) and other blood incompatibility: Rh incompatibility occurs when an Rh negative mother becomes pregnant with an Rh positive child. In this scenario, maternal Rh antibody, which can cross the placenta and the immature fetal blood–brain barrier, binds to fetal Rh antigens, causing hemolytic disease of the newborn, which includes neurodevelopmental consequences (Bowman, 1999). In this section, we review studies of Rh and other blood incompatibility in schizophrenia (Table 2).

In the first known study of Rh incompatibility and schizophrenia, Hollister et al. (1996), in a Danish cohort, found that Rh incompatibility was associated with a nearly three-fold increased risk of schizophrenia in male offspring. The risk was present only in second or later born offspring, which is consistent with the literature on hemolytic disease of the newborn. These outcomes are rarely seen in first born offspring, since Rh sensitization by a previous Rh incompatible pregnancy is generally necessary for sufficient maternal Rh antibody to develop. In a second study, using a candidate-gene approach with patient-parent pairs and trios drawn from a Finnish sample, a greater than two-fold increased risk of schizophrenia was observed when there was incompatibility between maternal and fetal genotypes (Palmer et al., 2002). In a third study, based on the CHDS birth cohort, in northern California, Insel et al. (2005) found a nearly two-fold, though non-significant increase in risk of schizophrenia among Rh incompatible offspring; a significant sex by exposure interaction was observed, with a greater than three-fold increase in male offspring. A modest increase in risk of schizophrenia was also observed for ABO incompatibility (involving a mother with blood type O and offspring with either A or B blood types), and a significant interaction effect was demonstrated between sex and exposure. If Rh incompatibility is proven to be a cause of schizophrenia, this would suggest that anti-Rh (D) prophylaxis, an obstetric practice which prevents sensitization in Rh-negative women, and has already been routinely implemented in many countries, would be expected to diminish not only hemolytic disease of the newborn, but also the risk of schizophrenia.

3.1.7.3. Maternal stress—Several studies suggest that the mother's experience of stress during pregnancy may be related to an increased risk of schizophrenia in offspring (Table 3). In two studies, the offspring of mothers who experienced death or serious illness of close family members exhibited an increased risk of schizophrenia (Huttunen and Niskanen, 1978; Khashan et al., 2008), although the apparent periods of exposure during pregnancy differed between the two studies. Ecologic designs have explored the effect of events during pregnancy that are generally deemed to be stressful on risk of schizophrenia in offspring. Invasion of the Netherlands by Germany in World War II during the first and second trimesters was related to an increased risk of schizophrenia among offspring (van Os and Selten, 1998). Exposure to the Israeli Six Day War during pregnancy was associated with increased schizophrenia risk in female offspring following exposure in the second month of fetal life (Malaspina et al., 2008). Not all studies of maternal stress and offspring risk of schizophrenia have yielded significant effects, however. In a study of mothers who experienced a severe flood in the Netherlands, an increased risk of schizophrenia was observed, but the finding was not statistically significant (Selten et al., 1999).

Two birth cohort studies of schizophrenia have capitalized on data collected during gestation on wantedness of pregnancy, which may be associated with maternal stress. These studies found that mothers who reported the pregnancies as unwanted were more likely to have offspring who later developed schizophrenia (Herman et al., 2006; Myhrman et al., 1996). It should be noted that the investigators' intention for studying "unwanted pregnancy" was *not* to test hypotheses on quality of child rearing, but was rather focused on prenatal stress and the effects of various other hardships to the mother during pregnancy.

While the studies of individually documented maternal experiences believed to be related to stressful life events represented an advance over the ecologic designs, which are based on population-level data, they are nonetheless hampered by a lack of direct measures of stress, including the mother's ability to adapt to these events. Furthermore, an inherent difficulty of these studies relates to the precision of timing of relevant exposures. It is likely that the stressful effects of loss of a loved one, or the consequences of an unwanted pregnancy extend beyond the period during which these events occurred or were reported. Hence, future studies will be needed to more precisely define the type and gestational timing of prenatal stress, and to evaluate the physiological effects of these stressors. The use of maternal biomarkers of stress could represent a promising strategy to address these issues.

If maternal stress during pregnancy is confirmed as a *bona fide* risk factor for schizophrenia, this raises interesting questions about the potential biological mechanisms. Stressful life events have been associated with low birthweight (Khashan et al., 2008; Wadhwa et al., 2004), which has been consistently related to an increased risk of schizophrenia (see Section 3.1.6). These effects might be mediated by maternal or fetal levels of glucocorticoids. Elevated levels of corticotrophin-releasing hormone (CRH) in late pregnancy were shown to be related to small for gestational age (SGA) status of the newborn (Wadhwa et al., 2004). In addition, maternal cortisol elevations in early to mid-gestation were associated with diminished physical and neuromuscular maturation, and to increased placental CRH in late gestation, which also increased risk of maturational deficits in the infant (Ellman et al., 2008). Maternal stress and glucocorticoids have also been shown to have effects on immune functioning, although studies have suggested both anti-inflammatory and pro-inflammatory consequences (Farina and Winkelman, 2005). Potential activation of the pro-inflammatory response would be consistent with previous studies indicating that maternal infections and immune activation (Brown and Derkits, 2010; Patterson, 2009) are potential risk factors for schizophrenia (see Section 3.1.3).

Animal models of prenatal stress aiming to test the biological plausibility of this exposure as a risk factor for schizophrenia have utilized restraint and variable stress models. These models, based on studies of rodents, have been reviewed recently by Meyer and Feldon (2010). Exposure to variable maternal stress was related to potentiated amphetamine sensitivity and impaired sensorimotor gating in offspring (Koenig et al., 2005); these effects were only observed following puberty. Repeated restraint stress has also been shown to cause a hyperlocomotor response to novelty or amphetamine (Deminier et al., 1992). Unlike variable stress, repeated restraint stress had no effect on sensorimotor gating in adult offspring (Burton et al., 2006; Lehmann et al., 2000). Prenatal stress paradigms have also revealed impaired working memory (Gue et al., 2004) and reversal learning (Kapoor et al., 2009) in offspring. Most of the effects of prenatal stress were observed in male but not in female offspring (Koenig et al., 2005). Additional studies involving maternal administration of endogenous glucocorticoids have demonstrated enhanced spontaneous locomotor activity (Diaz et al., 1997), amphetamine hypersensitivity, and a disrupted locomotor response to apomorphine, a direct dopamine agonist.

Primate studies have also provided evidence that prenatal stress has an impact on brain development that may be relevant to the pathogenesis of schizophrenia. Coe et al. (2003) found that administration of early and late stress in pregnant rhesus monkeys by an acoustic startle paradigm caused a significant, marked decline in density of bromodeoxyuridine (BrdUrd)-labeled cells in the dentate gyrus of offspring at 2.5–3 years of age, as well as a trend for a decline in the hilus, indicating a reduction in neurogenesis in these brain regions. Prenatal stress during both early and late pregnancy also led to a significant decrease in hippocampal volume in offspring. Moreover, the authors observed that maternal stress resulted in significantly higher basal and dexamethasone-induced cortisol levels in offspring. The authors conclude that prenatal stress may influence the plasticity of neural circuitry in offspring, which may alter the stable integration of a low number of newly generated neurons into existing neural networks. Prenatal stress could also lead to lifelong alterations of the HPA axis which may explain in part the impaired responses of schizophrenia patients to stressful life events (Harris and Seckl, 2010).

3.2. Specific environmental factors documented during childhood and adulthood

Specific environmental factors identified during the childhood, adolescent, and adult periods have also been investigated in relation to risk of schizophrenia. The four that have been most frequently studied are cannabis use, socioeconomic status, childhood trauma and infectious agents. These will be elaborated below.

One key issue in common with these and other environmental exposures that occur during childhood or later is the direction of cause and effect. Essentially, the question that arises is whether the environmental exposure causes schizophrenia, or whether schizophrenia or associated factors, lead to the environmental exposure. This limitation is not as prominent of an issue for studies of prenatal exposures since the individual cannot influence its in utero environmental milieu, although this assumes that a prenatal exposure is not correlated with the same exposure later in life.

3.2.1. Cannabis—In this section, we review findings on adolescent cannabis use as a risk factor for later schizophrenia (see Table 4). In a cohort study of over 40,000 Swedish conscripts followed up for 15 years, a two-fold increase in risk of schizophrenia was observed for subjects who had smoked cannabis by the age of conscription (Andreasson et al., 1987; Zammit et al., 2002), and the findings persisted in a subsequent follow-up of the cohort 27 years later. Another significant finding of the study is the “dose-response” relationship, in which a six-fold increased risk of schizophrenia was observed among heavy cannabis users, as compared to nonusers (Zammit et al., 2002).

These findings were replicated in several studies. van Os et al. (2002), in a population-based prospective study in the Netherlands demonstrated a nearly three-fold effect of cannabis use on risk of psychotic symptoms in over 4000 subjects followed up for three years, and a dose-response effect was also observed. In that study, baseline lifetime cannabis use more strongly predicted psychosis than use during the follow-up period. Subjects who had evidence of susceptibility to psychosis had a much more robust increase in risk of psychosis with cannabis use than those who did not.

Further confirmation of these findings was observed in two birth cohort studies, both from New Zealand. In the Christchurch study (Fergusson et al., 2003), which took place over more than 20 years, cannabis dependence disorder at age 18 years was related to a two-fold increased risk of new psychotic symptoms, and the finding persisted after adjustment for prior psychotic symptoms. In the Dunedin study, another longitudinal birth cohort investigation from New Zealand, use of cannabis at age 15 was associated with a greater than four-fold increase in risk of schizophreniform disorder at age 26 (Arseneault et al.,

2002). Adjustment for childhood psychotic symptoms diminished the effect to a nonsignificant, approximately three-fold risk. In a study by Henquet et al. (2005), of nearly 2500 subjects followed up over four years in Germany, use of cannabis was related to a 1.7-fold increase in psychotic symptoms; interestingly, vulnerability to psychosis at baseline was not related to cannabis use at follow-up, suggesting that the subjects were not using cannabis to alleviate the psychotic symptoms. Pooled odds ratios from meta-analyses yielded effect sizes ranging from 1.4 to 2.1 (Henquet et al., 2005; Moore et al., 2007).

In a review and meta-analysis of prospective studies of cannabis and schizophrenia, including most of those above, Arseneault et al. (2002) reported a pooled odds ratio of 2.3 (95% CI = 1.7–2.9). The authors argue for a potential causal effect based on evidence that cannabis use nearly always preceded onset of schizophrenia, persistence following adjustment for numerous confounders, and a dose-response relationship. Nonetheless, they also note limitations of these studies, including varying definitions of psychosis outcome, reliance on self-reported cannabis use, lack of information on potential confounding effects of other illicit drug use, and prodromal symptoms that could lead to reverse causality (an issue that was addressed in the Dunedin study cited above).

Intriguing findings suggest that cannabis use may interact with genetic vulnerability to lead to psychosis. Caspi et al. (2005) found that a variation in the catecholamine-O-methyl transferase (COMT) gene [a valine (Val) to methionine (Met) substitution at codon 158 (Val¹⁵⁸Met)], which increases release of prefrontal dopamine into synapses by decreased metabolism of dopamine, increases the effect of adolescent cannabis use on risk of subsequent schizophreniform disorder. Subjects with the Val/Val genotype had the greatest risk, followed by Val/Met subjects, and Met/Met individuals had no increase in risk. This also suggests a potential pathophysiological mechanism for the effects of cannabis involving enhancement in dopamine activity in susceptible individuals. In a subsequent study, subjects with the homozygous Val genotype with previous evidence of psychosis liability had an increase in cannabis-induced psychotic symptoms (Henquet et al., 2006).

Cannabis is the most potent agonist on the cannabinoid receptor 1 (CB₁). Excessive stimulation of CB₁ receptors on GABAergic and glutamatergic nerve terminals regulate dopaminergic projection firing from the brain stem to the striatum. In one proposed pathophysiologic mechanism for schizophrenia, cannabis is postulated to block inhibitory inputs onto dopaminergic neurons (Morrison and Murray, 2009).

3.2.2. Socioeconomic status—It has long been known that patients with schizophrenia are overrepresented in the lowest social strata (Eaton, 1985; Hollingshead and Redlich, 1958). This has led investigators to propose two competing hypotheses to explain this observation: social causation versus social drift. The social causation hypothesis asserts that schizophrenia is a result of low social class and the many psychosocial and biologically based environmental exposures that accompany this environment; the latter hypothesis argues that individuals with schizophrenia are more likely to migrate to low socioeconomic neighborhoods (Dohrenwend et al., 1992). To test this hypothesis, studies investigated whether social class at birth (generally defined as paternal social class) was related to risk of schizophrenia. These studies generally found either no association (Goldberg and Morrison, 1963; Hare et al., 1972; Timms, 1998), or occasionally higher social class of origin (Jones et al., 1994a; Makikyro et al., 1997; Mulvany et al., 2001; Wiersma et al., 1983) among subjects who later developed schizophrenia; these studies included population-based cohort investigations. Nonetheless, two recent papers suggest that there may be some effect of social class on schizophrenia risk. Wicks et al. (2005), in a Swedish birth cohort, demonstrated that several factors related to low social class, including parental unemployment, receipt of social welfare, and single-parent households were related to

higher schizophrenia risk in offspring. In the Jerusalem Perinatal Study, a small increase in risk was observed for schizophrenia in subjects whose fathers were in the lowest stratum of social class at birth, but there was no social class gradient on risk of the disorder (Corcoran et al., 2009). Hence, evidence supporting the social causation hypothesis is inconclusive.

3.2.3. Childhood trauma—Evidence from several studies has identified childhood trauma as a putative risk factor for schizophrenia. In a recent review, Morgan and Fisher (2007) discuss previous studies and address the limitations of this work. While a number of studies have reported an increased prevalence of childhood trauma among subjects with psychotic disorders, these studies were limited by small, highly selected, and heterogeneous samples, and by variations in the measures of abuse. Population-based studies aimed at surmounting at least some of these limitations have offered more promise. In the British National Survey of Psychiatric Morbidity, Bebbington et al. (2004) observed a nearly three-fold increase in risk of a definite or probable psychotic disorder following sexual abuse at some point in the lifetime, adjusting for other negative life events and depression. Janssen et al. (2004), in the Netherlands, reported that emotional, physical, and sexual abuse before age 16 was related to a seven-fold increase in psychotic symptoms, although the number of cases was small. In a similarly designed study, an association was found between any lifetime trauma, including sexual abuse, and the development of 3 or more psychotic symptoms (Spauwen et al., 2006). As noted by the authors of the review, each of these studies, however, was hampered by imprecise measures of trauma, including retrospective assessment, which can lead to recall bias, and most of these studies relied upon reports of psychotic symptoms, rather than a diagnosis of schizophrenia (Morgan and Fisher, 2007). In the lone study that employed contemporaneous, official records, Spataro et al. (2004) reported that sexual abuse before age 16 was not associated with hospital admission for schizophrenia. However, this study was limited by the probable absence of most cases of sexual abuse in records from government authorities. A final limitation noted by the authors is that positive symptoms occur among individuals with post-traumatic stress disorder, which may be co-morbid with schizophrenia. Hence, while childhood trauma is a major societal and public health issue and is potentially plausible as a risk factor for psychosis, it is probably premature to draw substantive conclusions about a causal relationship with schizophrenia.

3.2.4. Infections documented in adolescence and adulthood—In contrast to the studies of prenatal infection and schizophrenia, a substantial number of investigations have examined the relationship between infection and schizophrenia in patients who have already developed the disorder (Yolken and Torrey, 2008). In a meta-analysis of 23 studies *T. gondii* infection in schizophrenia patients, based on quantification of antibody to this agent, a greater than two-fold increased risk was observed (Torrey et al., 2007). Although these findings are intriguing, the cross-sectional methodology of the studies raises the question as to the direction of causality. As discussed in Yolken and Torrey (2008), while *T. gondii* could be a potential cause of schizophrenia, it is also possible that concomitants of schizophrenia, including hospitalization and lifestyle differences, could predispose to contact with the organism, and these factors, as well as medications, could modify the host immune response to the infection, making the individual more susceptible to its acquisition. A second methodologic issue is the potential for selection bias, given that in many of these studies controls were not selected from a source population that would give rise to cases, resulting in findings which could be confounded by demographic and other factors that are related to both *T. gondii* and to schizophrenia.

Two notable studies have attempted to address these limitations. The first involved toxoplasma IgG antibody levels to individuals who were at “ultra-high risk” for psychotic disorders (Amminger et al., 2007). This study included subjects with genetic risk, attenuated

symptoms, and/or brief, limited intermittent psychotic symptoms. The authors found that seropositivity for toxoplasma was significantly associated with greater severity of psychotic symptoms, and a correlation was observed between level of IgG antibody and severity of psychotic subscale scores on the Brief Psychiatric Rating Scale. Given that these subjects had not converted to a psychotic disorder, it is less likely that concomitants of these disorders may have caused the elevated toxoplasma antibody titers. In a second study, which made use of archived serum specimens from US military recruits, toxoplasma IgG antibody levels drawn within 6 months of diagnosis were associated with a significant, modestly increased risk of schizophrenia, but no increased associations were observed in serum samples drawn prior to 6 months before diagnosis (although a statistical trend was observed for an association in samples drawn 2–3 years before diagnosis) (Niebuhr et al., 2008). A limitation, noted by the authors, is that the antibody levels and the outcomes were not assessed longitudinally.

The other major microbial agent investigated in relation to schizophrenia in adult patients is cytomegalovirus (CMV). The results of these studies have been mixed, with 5 studies demonstrating increased CMV seropositivity among patients with more recent onset of schizophrenia, but 14 negative studies. It has been noted, however, that the assay methods in the positive studies were more sensitive than those of the negative studies (Torrey et al., 2006). Elevated antibody to CMV has been associated with deficit symptoms in schizophrenia patients (Dickerson et al., 2006). Studies of CSF IgG for CMV have also been mixed (Yolken and Torrey, 2008).

Another approach to sort out cause and effect relationships, and, more importantly, to translate these associations to effective treatments, is to examine whether agents that suppress these infections lead to improvement of symptoms. In a 16-week, double blind clinical trial, valacyclovir, an antiviral medication given as an adjunct to antipsychotic medications, was related to significant improvement in overall symptoms (Dickerson et al., 2003), including positive symptoms, among seropositive subjects; however, this was not replicated in a subsequent study (Dickerson et al., 2009). A trial of adjunctive azithromycin, a broad-spectrum antibiotic with anti-toxoplasma activity, in *T. gondii* seropositive schizophrenia cases, also did not produce improvement in symptoms (Dickerson et al., 2009). Clearly, this work will require testing of further antimicrobials with more specific or potent effects on inhibition of the infection. It should be kept in mind, however, that if infections such as *T. gondii* or CMV have already resulted in neuromorphological or neurochemical alterations, eliminating the infection may not necessarily reverse the neuropathology that gives rise to symptoms. If this is true, then it would suggest that approaches aimed at primary prevention, or treatment of prodromal or first-episode cases may prove to be more effective. It is also unclear whether these medications would need to be given long-term; in the case of antibiotics, this may not be advisable.

4. Synthesis and implications of the findings

In summary there is rapidly accumulating evidence that environmental exposures, operating as early as the periconceptional period of pregnancy, and potentially as late as adolescence or adulthood, could play an important role in the susceptibility to schizophrenia. This runs counter to the prevailing view that schizophrenia is primarily a genetic disorder, an assertion which is largely derived from heritability estimates, which, as noted earlier, may have yielded an inflated estimate of the relative contribution of the genetic contribution to schizophrenia. An emphasis on genes may have also originated from results of early studies of environmental factors in schizophrenia. These consisted largely of proxy measures of environmental exposures, including ecologically derived data on infections and measures of 'obstetric complications,' from sources that were less precise, not systematically recorded,

and derived from case-control studies rather than population-based cohorts. Consequently, several of the findings from this initial work were not replicated and may have also underestimated the relative contribution of environmental factors to risk of schizophrenia.

Since those earlier studies, newer investigations have introduced more refined approaches, including objective measures of environmental exposures, such as infectious, nutritional, and toxic insults, obtained from prospectively acquired biomarker data, detailed obstetric records, and data from postnatal life that were collected for research purposes. Research designs on sociocultural risk factors have also progressed, including carefully conducted studies of immigration and neighborhood status in well-diagnosed incident cases.

As discussed in this review, there is ample evidence from preclinical studies that environmental exposures, particularly those operating during the in utero or early neonatal periods, produce phenotypes that resemble behavioral and brain anomalies of patients with schizophrenia, and the putative biological mechanisms implicate similar neurochemical and neuromorphological substrates as those observed in prior studies of schizophrenia (Meyer and Feldon, 2010). Although caution is warranted in the extrapolation from animal to human data, the findings on effects of environmental insults in many animal models of schizophrenia appear to be as persuasive as those from studies of genetic manipulations, such as knock-out studies.

Although carefully conducted studies of environmental exposures in schizophrenia are generally less numerous than corresponding studies of genetic factors, there are compelling reasons to believe that further investment in studies of the 'envirome' as a strategy for elucidating the underpinnings of this disorder is justifiable. First, although more work is necessary, the effect sizes observed in positive epidemiologic studies of risk factors for this disorder have thus far been stronger than those derived from studies of individual susceptibility genes. Second, as noted above, the biological plausibility and coherence of the findings from the environmental literature mirror those for genetic variants in the disorder. Third, as discussed below (Section 4.1), the identification of environmental origins of schizophrenia is readily translatable to direct public health interventions.

4.1. Prevention

One key implication of the discovery of environmental etiologies of schizophrenia is prevention. There are already many public health approaches to reducing or eliminating exposure to several of the environmental exposures discussed above. With regard to microbial agents, for example, influenza vaccination is a cornerstone of the prevention of infection with this pathogen, and many genital/reproductive infections are treatable with antibiotics and preventable by use of barrier contraceptives. Folic acid supplementation during pregnancy has already been demonstrated to reduce the incidence of neural tube defects (Graham, 1997) and is routinely given during pregnancy and is used universally in the fortification of breads and cereals. Iron supplementation has also long been administered to pregnant women to improve maternal and fetal health. Improvements in perinatal care, including new interventions in premature infants, and use of anti-Rh-D prophylaxis (Liumbruno et al., 2010) to eliminate the maternal Rh antibody response reduces morbidity and mortality and is expected to have already reduced the incidence of neurodevelopmental disorders. The reduction of exposure to lead through unleaded gasoline and the removal of lead from paint has markedly decreased lead levels in the population (Meyer et al., 2008a). At the psychosocial level, efforts are underway to reduce economic, medical, social, and occupational disparities, including successes at reducing racial discrimination and its effects (Smedley, 2006). If any or all of these exposures are truly associated with schizophrenia risk, it is conceivable that we might expect to see a reduction in risk of schizophrenia in the coming years. In fact, one of the reasons given for the decline in schizophrenia incidence

over time in a study by Suvisaari et al. (1999b) is the introduction of improvements in perinatal care and reduction in exposure to infectious microbes.

How does one quantify the impact of measures aimed at reducing environmental exposures in a population? One such statistic is known as the population attributable proportion (PAP). The PAP is defined as the percentage of cases of a disorder among a population that would be prevented conditional on complete removal of an exposure from the population. The PAP is calculated from the effect size of the exposure on risk of the outcome and the population prevalence of the risk factor (Rothman and Greenland, 1998). As an example, the PAP corresponding to complete removal of three prenatal infections (influenza, toxoplasma, G/R infections) associated with schizophrenia in our previous work was as high as 33%. For the urban birth and season of birth risk factors, the PAP's, respectively were approximately 30% (Marcelis et al., 1998; McGrath and Scott, 2006; Mortensen et al., 1999) and 3.3% (though as high as 10.5% in one study) (Davies et al., 2003; Mortensen et al., 1999). In the case of infection and urbanicity, the high PAP's are due both to the relatively high prevalence of these exposures in the population, and the considerable effect sizes. These PAP's are considerably larger than those for most genetic variants. This indicates that if public health efforts become capable of full removal of these infections from the population, one would expect that the incidence of schizophrenia in the population would decline by as much as one-third. While it is unlikely that such an achievement could be realistically accomplished, and further attempts toward replication of these findings will be necessary, this figure suggests that even partial reduction of exposure to these infections could have an appreciable impact on reduction in risk of this disorder. Many of the other categories of preventable risk factors cited in this manuscript are also present in a substantial proportion of the population. These include folate and iron deficiency, and exposure to lead paint in old buildings; these problems are particularly prevalent among the lowest social classes.

4.2. Toward a coherent theory of the etiopathogenesis of schizophrenia: developmental mechanisms

The study of environmental factors in schizophrenia also offers the potential to complement, and refine, existing efforts on explanatory models of the etiopathogenesis of schizophrenia. Most models of schizophrenia are based on a neurodevelopmental perspective, and are organized around three central themes. The first, known as the “static” model, posits a primary insult during pre- or perinatal life, which occurs during a critical period of brain development, remains latent following the event, and becomes “activated” by normal neurodevelopmental processes. This model was initially proposed by Weinberger (1987), who argued that a latent developmental brain lesion interacts with normal development of prefrontal dopaminergic circuitry during adolescence, contributing to the overt manifestations of psychosis. Further supporting evidence for this conjecture relates to the marked decline in the number of excitatory synapses in the cerebral cortex in the peri-adolescent period, known as “synaptic pruning,” and an increase in myelination of prefrontal-limbic circuitry at this time of development. The second model is based on the assertion that a deviation in brain maturation during adolescence, such as an impairment in the process of synaptic pruning (Feinberg, 1982), due either to abnormal programming or to an exogenous factor, sufficiently disrupts the neurodevelopmental trajectory, either by itself, or through interactions with early life events, to predispose to development of overt psychosis.

Adapting aspects of a third model, which incorporates aspects of the two aforementioned models, as elaborated by Lewis and Levitt (2002), an early brain lesion results in a cascade of events that occur throughout childhood and adolescence, becoming more exacerbated during critical periods, to alter the developmental trajectory that ultimately results in the onset of schizophrenia. Based on evidence from developmental neurobiology, they posit that

early events, such as the formation of brain circuitry “occurs through a continuum of processes which change over time and which are highly dependent upon previous events to produce ultimately a normal functional state.” Several neurodevelopmental events, including neuronal and glial proliferation, migration, differentiation, and circuit assembly depend on complex interactions occurring intracellularly and between the neuron and its environment to regulate specific developmental processes. These processes are tied to the normal developmental time course of the affected neural systems, such that a deviation in the trajectory is most apparent during the period of development during which the neural substrates change most rapidly. For schizophrenia, developmentally specific processes that are known to occur between adolescence and early adulthood, including pruning of several brain regions (prefrontal corticocortical and cortico-subcortical synapses) (Feinberg, 1982; Keshavan et al., 1994; Lewis and Levitt, 2002), the reduction of synaptic density between childhood and adolescence (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997), and myelination of the subicular and presubicular regions (Benes, 1989), have been proposed to act as triggers for the onset of psychotic symptoms. Consistent with this model, neuroimaging studies of childhood onset schizophrenia have revealed an exaggerated, progressive reduction in cortical and subcortical gray matter volume during adolescence; this age-accelerated gray matter loss moved in a dynamic posterior to anterior gradient across the brain, from the parietal, to temporal, and finally to frontal brain regions, and was associated with expected patterns of psychotic symptoms and neurocognitive deficits (Thompson et al., 2001). This may be consistent with large-scale synaptic elimination during this period.

The role of environmental risk factors in the etiopathogenesis of schizophrenia can be further clarified by mapping them on to a known developmental trajectory. To illustrate how a prenatal brain insult can interact with later neurodevelopmental processes, we elaborate on empirical evidence from a study by our group on in utero exposure to rubella (Brown et al., 2001) (see Fig. 1).

As noted above (see Section 3.1.3.2.1), our group has demonstrated, in a birth cohort study, that offspring of mothers exposed to rubella during pregnancy evidenced a markedly increased risk of schizophrenia and other schizophrenia spectrum disorders (Brown et al., 2000a, 2001). We observed that nearly 90% of cases of schizophrenia/spectrum disorder in this rubella-exposed cohort evidenced a decline in IQ between childhood and adolescence, compared to only 37% of the rubella-exposed subjects who did not develop major psychiatric disorders. This decline was in excess of what was observed during childhood, in which IQ was mildly decreased in subjects who later developed schizophrenia. Viewed from a neurodevelopmental perspective, these findings suggest that events that occur both during the prenatal and adolescent periods may account for the observed relationship between prenatal rubella and risk of schizophrenia. During the prenatal period, rubella is known to cross the placenta and the fetal blood brain barrier, where it inhibits mitosis, resulting in hypocellularity and diminished brain growth, and retards myelination due to reduced replication of oligodendrocytes (Kemper et al., 1973). Moreover, rubella induces a proinflammatory response, resulting in ischemic damage (Rorke et al., 1968; Townsend et al., 1994). The period of gestation which is most vulnerable to the classic developmental sequelae of rubella, and to schizophrenia, is the first trimester (South and Sever, 1985).

Considered from the standpoint of the Weinberger (1987) model, the subjects in this study experienced a pathogenic brain lesion, including a deficit in neuronal and synaptic number and manifesting as a mild IQ deficit in childhood. The deterioration in IQ in subjects who later developed schizophrenia/spectrum disorders may have resulted from an interaction between this early brain lesion and functional maturation of brain regions that subserve IQ, which included a decline in synaptic density. In this model, schizophrenia could result from

the normally expected reduction in synapses acting upon an already deficient synaptic reserve due to the in utero insult.

From the perspective of the other aforementioned pathogenic models, it can be argued that a brain lesion induced by prenatal rubella unleashes a cascade of events which include an exaggeration of programmed synaptic elimination between childhood and adolescence. Curiously, Huttenlocher (1979) observed a decline of synaptic density between the same ages during which the rubella-exposed subjects were assessed in our study. The observed findings may also be explained by a predisposition to an abnormal myelination process during adolescence due to reduction in myelination expected at birth.

4.2.1. Mediating pathways—An additional consideration in a model of pathogenesis involving environmental factors are putative pathways by which these insults may act to disrupt neurodevelopment at different stages of life. One attractive hypothesis is that different environmental factors act to increase risk of schizophrenia through common mechanisms that interact with developmental events such as those described above. Investigators have previously hypothesized that environmental insults converge on a number of pathogenic processes, including oxidative stress, apoptosis, inflammatory processes, and HPA-mediated mechanisms.

4.2.1.1. Oxidative stress: Do et al. (2009) have argued that the effects of many environmental factors, including malnutrition, toxins, infections, OC's, and psychosocial stress, on risk of schizophrenia may be mediated by transient or long-term oxidative and nitrosative stress, involving an imbalance between overproduction of reactive oxygen species (ROS) and deficiency of enzymatic and non-enzymatic antioxidants, and diminished glutathione (GSH), a tripeptide which protects against oxidative stress. This creates harmful (per)-oxidation of lipids, proteins, and DNA. Consistent with this hypothesis, their work has demonstrated lower levels of GSH in patients with schizophrenia. Oxidative stress during development has been demonstrated to cause NMDA receptor hypofunction and deficient myelination (Do et al., 2009).

4.2.1.2. Apoptotic mechanisms: Apoptosis is a highly regulated form of cell death that is pervasive in fetal brain development and that eliminates injured or diseased neurons during the lifespan (Jarskog et al., 2004). This mechanism has been invoked in the etiopathogenesis of schizophrenia to account for evidence of neuronal or synaptic/dendritic loss in the absence of cortical gliosis in postmortem studies. A decrease in levels of Bcl-2, an anti-apoptotic regulatory protein, was observed in middle temporal gyrus of postmortem brain of patients with schizophrenia (Jarskog et al., 2000). Such a reduction may reduce the protection of neurons against pro-apoptotic insults. Although levels of caspase-3, a marker of apoptosis, were not increased in temporal lobe (Jarskog et al., 2004), the authors speculated that apoptotic activity could contribute to progressive neurostructural alterations in prodromal and first-episode psychosis in response to a time-limited increase in pro-apoptotic stimuli, including fetal or perinatal insults. Several environmental or environmentally induced factors that are pro-apoptotic including ischemia, hypoxia, pro-inflammatory cytokines (Thompson, 1995), and oxidative stress (see Section 4.2.3).

4.2.1.3. Inflammatory mechanisms: Pro-inflammatory cytokine release is described above as a common mediator of infectious insults (see Section 3.1.3.2.1). However, inflammatory processes, which also include secretion of prostaglandins and other immune modulators, can be induced by a variety of other environmental insults, including tissue injury and hypoxia (Guo et al., 2010), and prevented by certain micronutrients including omega-3 fatty acids (Ruggiero et al., 2009).

4.2.1.4. HPA axis: Activation of the HPA axis represents a common reaction to many environmental insults discussed above, including infection, malnutrition, and hypoxia, and, not surprisingly, stress-related pathways (Oitzl et al., 2010). HPA hyperactivity may also mediate the effects of psychosocial factors that have been associated with schizophrenia, including migration, living in hostile or dangerous neighborhoods, and low socioeconomic status. Putative biological mechanisms by which stressors may increase risk of schizophrenia are discussed in Section 3.1.7.4.

4.2.1.5. Other relationships between environmental exposures: Furthermore, even a cursory review of many of the environmental factors discussed above in relation to schizophrenia will suggest mechanistic interactions between them. For example, respiratory infection, maternal anemia, or elevated homocysteine could act to increase risk of schizophrenia by inducing acute or chronic fetal hypoxia (Gunn and Bennet, 2009), and several types of malnutrition can increase the risk of infection by compromising immune function (Cunningham-Rundles et al., 2009). Moreover, certain cooccurring risk factors, such as omega-3 fatty acids (Yashodhara et al., 2009) and environmental toxins such as PCB's, which are both found in fish (Boucher et al., 2009), may have protective, and risk increasing effects, respectively.

This challenge can be addressed by epidemiologic studies with rich datasets and large sample sizes which offer the potential to delineate the mediating, confounding, and moderating effects of co-occurring environmental factors involved in schizophrenia.

5. Future studies

Notwithstanding the intriguing findings presented above, this field of research is still in a relatively early phase. In this section, we propose several steps for future work that will be needed to substantiate the hypotheses, extend this research to investigations of genetic and epigenetic effects, integrate epidemiologic research with clinical neuroscience approaches, and progress further on translational research.

5.1. Future epidemiologic studies

5.1.1. Limitations of previous research efforts—Clearly, it will be essential to independently replicate the findings of the epidemiologic studies in other cohorts and samples. Moreover, the environmental exposures investigated to date in relation to schizophrenia risk may represent only the 'tip of the iceberg.' Although there have been substantial methodologic advances in many studies in this field, including the use of archived biospecimens, prospectively acquired data, and detailed datasets, a number of limitations may temper causal inferences drawn from the results.

First, while many of the epidemiologic studies were based on large population-based samples, the relatively infrequent occurrence of schizophrenia often led to small to modest sample sizes of cases. This may have reduced statistical power to detect effects of certain exposures. In several studies, small sample sizes may have diminished the precision of the effects observed, reflected by relatively wide confidence limits. Small sample sizes also reduced the possibility for investigating less common exposures. Although rare, these exposures may act additively, or interact with susceptibility genes. There may also be additional environmental factors that are rare, but have large effects on risk of the disorder, as exemplified by prenatal exposure to rubella. This may be analogous to the large effect sizes observed for highly penetrant copy number variants (CNVs) (Kirov et al., 2009) on risk of schizophrenia. Curiously, these CNVs predispose to a variety of outcomes in addition to schizophrenia, including neurodevelopmental disruptions such as mental retardation, cataracts, deafness, and other psychiatric disorders, all of which have been found in

offspring exposed prenatally to rubella. Low sample sizes also preclude the ability to test for gene-environment interaction (see Section 5.2), and to examine interactive and mediating effects of other exposures (see Section 4.2.1).

In future years, new birth cohorts will be available to investigate the hypotheses enumerated above with much larger sample sizes than those of previous cohorts. These cohorts include the Finnish Prenatal Studies (FiPS), the Danish National Longitudinal Study (DNLS) (Olsen et al., 2001), and the Mother and Baby Study (MoBA) in Norway (Magnus et al., 2006). The number of cases expected from these cohorts are expected to be orders of magnitude larger than in previous studies. For example, the total population of pregnancies in the FiPS is 1.5 million.

A second limitation is the methodology for measurement of the environmental exposures. Studies that rely on population-based prospectively followed cohorts with biomarker-based data or data that derived from detailed obstetric records are clearly more methodologically sound than those which rely on ecologic data, general measures of classes of exposures (e.g., stress, famine) and maternal recall of events, as well as cross-sectional investigations. In our view, the field needs to primarily focus on specific environmental risk factors and their interrelationships with other antecedents in the context of well-documented macrosocial events. An additional issue relates to the validity and reliability of the measures. Care needs to be taken with regard to the bioassay methodology (for biomarkers) and to the validity and reproducibility of the measures (for all environmental exposures, including those derived from interviews and records). Finally, it is worth noting that while the most novel and methodologically sophisticated approaches for the quantification of exposures are especially appealing, many standard assay methodologies, for example antibodies for exposure to infections, continue to be as, or even more informative, than newer approaches.

Third, attention needs to be paid to the potential for bias in the study design. This includes, but is not limited to biases arising from subject selection, loss to follow-up, and the collection of information. Selection bias can arise if the exposure-outcome associations in the sample selected for study are not representative of the source population. This can occur for several reasons, including incomplete ascertainment of cases or recruitment of non-representative controls in case-control studies. These problems can be obviated by the use of national birth cohorts from countries with centralized registries covering all or most cases in the country. Loss to follow-up represents a particularly important source of bias in studies requiring long-term follow-up, including disorders such as schizophrenia with long latency periods between the insult(s) and onset of the disorder. Bias can occur, for example if cohort members with certain exposures and early manifestations of schizophrenia leave the cohort at a greater rate than subjects without the exposure and the early manifestations.

These issues can be addressed by studies with population registries that contain systematically collected information and data on loss to follow-up, for example from migration. These registries include comprehensive psychiatric diagnoses and relevant characteristics of the source populations.

Fourth, the specificity of the relationship between environmental exposures and schizophrenia has not been adequately investigated in the published work. Fortunately, several studies are now examining associations between these exposures and bipolar disorder and autism, among others.

5.1.2. Environmental exposures and clinical neuroscience studies—In all of the studies cited in this review, schizophrenia has been considered as a unitary entity, based on the fulfillment of diagnostic criteria, which are identified by symptoms and signs of the

disorder. Yet, evidence from several areas of work, including recent genetic studies (Meyer-Lindenberg et al., 2006), suggests that investigations which directly investigate relationships between putative etiologies and brain structure and function may allow for the development and refinement of models proposed in Section 4.2. Such mechanisms disrupt neural anatomic circuitry and neurophysiologic functions, and these effects are likely modified by susceptibility genes and environmental insults. Although these concepts have been well accepted by much of the research community, most investigations of etiologic factors have not directly addressed these questions. To do so requires a redefinition of the phenotype from schizophrenia as a clinical disorder to a neurobiological phenotype which may overlap with other neuropsychiatric disorders.

Studies of environmental determinants of structural and functional brain phenotypes have only recently begun. In the Developmental Insult and Brain Anomaly in Schizophrenia Study (DIBS), our group has examined in utero and other early developmental exposures in schizophrenia cases and controls in the CHDS birth cohort. We found that maternal exposure to two serologically documented infections, influenza and anti-toxoplasma IgG, was significantly related to executive function deficits that are indicative of cognitive set-shifting ability (Brown et al., 2009b). In a magnetic resonance imaging (MRI) study, we demonstrated that maternal infection was related to markedly increased size of the cavum septum pellucidum, a neuembryological anomaly which has its origins during the prenatal or early postnatal period (Brown et al., 2009a). In the most recent of these studies, maternal cytokine elevations were positively correlated with CSF ventricular volume, the most commonly cited neuromorphological abnormality in schizophrenia (Ellman et al., 2010). We are proceeding with, and recommend, additional studies based on this paradigm.

This work builds on earlier findings demonstrating that fetal hypoxia is related to diminished hippocampal volume, decreased cortical gray matter volume, and other neuromorphologic anomalies in patients with schizophrenia (Cannon et al., 2002b; Van Erp et al., 2002).

Such studies may serve to provide validation of the environment-schizophrenia relationships at the biological level, suggest other neuropsychiatric disorders to be investigated in future work, define etiologically homogeneous subgroups with specific structural and functional neural deficits, and, in combination with animal models, yield essential data on neurobiological mechanisms and pathways.

5.2. Gene-environment interplay

Another especially promising direction for future work is on the interplay between genetic susceptibility and environmental exposures in schizophrenia. There are several paradigms which characterize the interplay between these factors. We focus on three such scenarios: gene-environment interaction, genes as antecedents of environmental exposures, and epigenetic effects.

5.2.1. Gene-environment interaction—While genes undoubtedly play an important role in the etiology of schizophrenia, and great strides have been made with regard to the methodology for gene identification, including genome wide association studies (GWAS), the effect sizes for even the strongest common genetic variants have been small (see Table 5). Moreover, many genes that have been replicated by more traditional genetic approaches have not been confirmed by GWAS (Purcell et al., 2009; Shi et al., 2009a; Stefansson et al., 2009). One reason for these small effect sizes and discrepancies is that environmental factors in genetically vulnerable individuals may be necessary for the expression of schizophrenia.

Gene-environment interaction refers to an increase in the effect of an environmental exposure in the presence of a susceptibility gene, compared to the absence of such a variant. If certain genes only increase risk of schizophrenia in the presence of an environmental exposure, this may complicate the search for genes because measurement of the environmental exposure would be necessary to detect the genetic effect.

Earlier, we discussed the potential interaction between variants in the COMT gene and cannabis use in predicting psychosis (see Section 3.2.1). Yet, few studies with high quality data have directly investigated interactions between susceptibility genes and environmental exposures in schizophrenia. One promising investigation, in a Finnish cohort, demonstrated a five-fold greater effect on risk of schizophrenia among offspring of mothers exposed to pyelonephritis during pregnancy in cases with a family history of psychosis compared to those with no family history (Clarke et al., 2009).

One strategy that may aid in the identification of candidate genes that interact with environmental exposures is the targeting of genes involved in neurodevelopmental processes, given the importance of the neurodevelopmental period in the etiology of schizophrenia. In fact, variants in two of the strongest candidate genes for schizophrenia, DISC1 and neuregulin, appear to have particularly important roles in neurodevelopmental mechanisms, especially during the *in utero* period (Brown and Derkits, 2010). In a previous publication, we discussed intriguing similarities between MIA and mutations in these two genes (Brown and Derkits, 2010). Moreover, recent animal studies have demonstrated that mutations in DISC1 and MIA interact to produce neuropsychiatric phenotypes that have been observed in schizophrenia (Ibi et al., 2010).

A second strategy is to target those genes that have been shown to be related to pathogenic processes for which a role of environmental exposures has been clearly identified. With regard to exposure to prenatal infection, genes that encode the MHC Class I proteins, which present antigens to T lymphocytes at the cell surface, represent intriguing candidates (Boulanger, 2009). These proteins play important roles not only in immune regulation, but also in brain development and function. Previous work has shown that certain MHC proteins are crucial for normal synaptic function, synaptic remodeling, and graded fine-tuning of plasticity. A potential role of MHC genes in schizophrenia is also supported by findings from three of the largest genome-wide association studies of schizophrenia: genetic variants in the extended MHC represented one of the few associations to reach statistical significance (Purcell et al., 2009; Shi et al., 2009a; Stefansson et al., 2009). Hence, a potentially useful approach would be to investigate MHC-related genes specifically in schizophrenia cases with a documented history of infection, in comparison to cases without a history of infection, and appropriate control groups.

A third strategy would be to adopt current high throughput approaches for interrogating the genome among subjects with documented environmental exposures related to schizophrenia. This may increase the signal of susceptibility alleles which interact with these exposures, thereby enhancing the potential for gene identification.

The preventive implications of these strategies also deserve comment. In the traditional model of gene-environment interaction, a putative genetic variant and a putative environmental exposure may each be necessary but are not in and of themselves sufficient causes of a (hypothetical) subset of schizophrenia cases. Under this scenario, altering the genetic variant may not be required to prevent the disorder in a predisposed individual. Rather, eliminating exposure to the environmental factor would probably represent a more practical and feasible approach. In other words, if gene-environment interaction is important in the etiology of schizophrenia, preventing environmental exposures could also reduce the

effects of susceptibility genes on risk of the disorder. Given the larger effect sizes and PAP's of several putative macro- and microlevel environmental risk factors (noted above) relative to those of individual susceptibility genes, it appears likely that public health approaches aimed at eliminating these exposures could have a greater effect on reducing the incidence of schizophrenia than approaches targeted at specific genetic modifications (see Table 5).

5.2.2. Genes as antecedents of environmental exposures—In this scenario, the effect of a susceptibility gene may be mediated by an environmental exposure to which the gene is causally related. One frequently cited example, initially presented from outside the framework of schizophrenia research, is that of a gene which predisposes to impulsive and reckless behaviors (Kendler and Eaves, 1986). Such a gene could, for example, increase the risk of head injury, with neuropsychiatric consequences. What is worth emphasizing in this case is that an association could be demonstrated between a genetic variant and a neuropsychiatric disorder without the variant having a direct effect on a pathogenic process in the brain. In this case, measuring the intervening environmental factor of head injury would identify a potential causal mechanism that accounts for the genetic association. As in gene–environment interaction, elucidation of this mechanism may have important implications for prevention. In this case, identifying individuals who are prone to impulsive behaviors and modifying them may be a more practical step than altering the genetic variant, and would preserve substantial resources aimed at investigating other causal mechanisms. It has been argued that this type of pathway may account for findings from heritability studies which have generally exhibited a small contribution of shared environment to the variance in the liability of the development of schizophrenia (Schwartz and Susser, 2006).

A second example of this type of gene–environment interplay is the association between a polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene and schizophrenia (Tan et al., 2004). The MTHFR mutation has been associated with low folate and high homocysteine levels, resulting from a disruption in metabolism of folate. Although a number of mechanisms have been proposed, one explanation involving an environmental component is that maternal expression of this mutated gene could alter fetal brain development by fetal exposure to low folate and/or high homocysteine (van der Linden et al., 2006). While one might observe an association between the MTHFR polymorphism and schizophrenia in the offspring, it is conceivable that this finding could be accounted at least in part by a genetically induced alteration in the maternal/in utero environment. Consequently, folate supplementation, which can enhance folate levels and diminish homocysteine levels even in those with the MTHFR mutation, has the potential to diminish risk of an outcome such as schizophrenia. In fact, for neural tube defects, which are prevented by maternal folate supplementation during pregnancy, it has already been demonstrated that there is a stronger association between the maternal MTHFR polymorphism and neural tube defects, than there is between the offspring MTHFR genotype and this outcome (van der Put and Blom, 2000).

5.2.3. Epigenetics—Epigenetics is the study of functional modifications to the genome that do not involve an alteration in nucleotide sequence (Zhang and Meaney, 2010). Epigenetic signals regulate the capacity of transcription factors to access the DNA, thereby modifying gene expression. This emerging science is particularly appealing to the study of environmental factors for several reasons. First, environmental exposures are known to alter the epigenome, and thus represent an intriguing pathway by which these factors interact with genes (Waterland and Michels, 2007). Second, epigenetic events have been implicated in early life 'programming,' as they are a mechanism by which an environmental exposure during critical periods of prenatal and postnatal development can lead to lifelong changes in gene expression and adult-onset disorders (see further description below). Third, epigenetics can account for the non-genetic transmission of phenotypic traits between generations.

The two most common epigenetic changes cited are DNA methylation and histone modifications. DNA methylation involves the addition of a methyl group onto cytosines and is a mechanism for the silencing of gene transcription (Bird, 1986; Holliday, 1989). Histone modifications involve an alteration in the local chemical properties of specific amino acids in the histone tails. For example, addition of an acetyl group to the histone tail loosens the association between the histones and DNA, thereby opening the chromatin and increasing the capacity for transcription factors to access DNA sites. This process results in active gene transcription (Zhang and Meaney, 2010).

The 'fetal programming hypothesis,' initially proposed by Barker (2004) is suggestive of a possible epigenetic influence of in utero environmental factors on adult health outcomes. This hypothesis derived from studies indicating a graded increase in risk of coronary heart disease with a decline in birthweight and weight at one year old, which persisted despite control for many confounders. This work was expanded to indicate that intrauterine influences played a role in other diseases including type 2 diabetes, stroke, and hypertension. Although a number of explanations were proposed to account for these findings, one of the most intriguing is epigenetic mechanisms. Waterland and Michels (2007) have asserted that environmental influences that alter transcriptional activity during the period in which DNA methylation is undergoing developmental changes can lead to permanent alterations in epigenetic regulation and consequent phenotypes, and propose experiments to test the developmental origins of disease hypothesis.

In further work on epigenetics, Meaney and colleagues (Zhang and Meaney, 2010), in rats, have demonstrated that the level of maternal tactile stimulation during the suckling period results in permanent changes in behavior and physiology of the offspring by effects on methylation at CpG sites in the promoter for the glucocorticoid receptor (GR). Offspring of high care-giving dams evidence almost complete demethylation at this site at postnatal day 6, compared to offspring of low care-giving dams, which have a permanent elevation in methylation at this site. The period of development from postnatal days 1–6 represents the critical ontogenic window. High maternal care during the early postnatal period causes activation of GR transcription, inducing permanent hypomethylation of the GR locus. Permanent derepression of GR transcription results from this hypomethylation, leading to appropriate behavioral and HPA responses to stress throughout life. In contrast, maternal stressors that decrease care to offspring are related to increased behavioral and HPA responses to stress by increasing methylation. This represents an excellent example of how an early epigenetic modification can result in a long-term behavioral phenotype.

It has been further argued that a major focus of epidemiologic studies that aim to identify systemic epigenetic modifications should focus on events that occur during the periconceptional period, given that epigenetic alterations in early embryonic development will be produced in diverse tissues (St Clair et al., 2005; Susser et al., 1996; Waterland and Michels, 2007). One of the first direct findings of epigenetic influences on long-term phenotypes was in the agouti mouse, which contains a metastable epiallele (A^{vy}) (Waterland, 2006). Interestingly, supplementation of folic acid, vitamin B12, betaine, and choline was shown to shift the coat color distribution of these mice from yellow to brown by causing hypermethylation of this epiallele.

In a recent MIA model, Smith et al. (2007) demonstrated that the cytokine interleukin-6 causes a dysregulation of brain gene expression, which persists into adulthood. Although the mechanisms that account for this observation have yet to be elucidated, an epigenetic process is very appealing. It is conceivable that epigenetic mechanisms may also explain the decreased expression of glutamic acid decarboxylase (GAD67), an important enzyme for GABA synthesis in cortical interneurons, in postmortem brain of patients with schizophrenia

(Akbarian and Huang, 2006; Costa et al., 2004). Diminished GAD67 expression in the chandelier GABA interneurons may explain disrupted synchronized cortical activity and impaired working memory in schizophrenia (Lewis et al., 2005). In GABAergic interneurons in postmortem brains of schizophrenia patients, DNA methyltransferase 1 (DNMT1), which increases methylation of cytosines by transfer of a methyl group from the methyl donor S-adenosyl-methionine (SAM) is increased (Veldic et al., 2004). Consistent with this finding, increased methylation in the promoter for the reelin gene, which is also expressed in GABAergic interneurons, has been observed (Abdolmaleky et al., 2005), and inhibition of DNMT1 in neuronal cell lines resulted in increased expression of both reelin and GAD67 (Kundakovic et al., 2007).

Although the study of epigenetic influences in schizophrenia is a novel field of endeavor, future epidemiologic studies offer the potential for demonstrating that early life environmental exposures could lead to schizophrenia by such effects (Smith et al., 2007). Testing of these hypotheses could be feasible in epidemiologic samples with prospective measurement of an exposure, and follow-up for epigenetic alterations in peripheral cells (such as leukocytes or fibroblasts) of patients with schizophrenia, particularly if the investigations focus on epigenetic changes that have been clearly demonstrated in animal models to be caused by environmental factors. Limitations of epigenetic studies in clinical samples have been described previously, and include the possibility that changes in gene expression in these peripheral cells may differ from those found in the central nervous system and abnormal epigenetic findings in postmortem brain samples may be secondary to insults occurring throughout the lifespan, creating difficulty in ascribing such alterations to environmental insults during specific periods of development.

5.3. Translational studies

As discussed earlier, translational approaches offer the potential to delineate the molecular mechanisms by which environmental exposures alter the development, structure, and function of neural circuitry that increase susceptibility to schizophrenia, and serve to provide validation of the epidemiologic associations, as they are free of bias and confounding. Animal models of several environmental exposures have helped to validate the epidemiologic findings by demonstrating brain and behavioral phenotypes that are analogous to those observed in schizophrenia. We recommend enhanced interdisciplinary efforts between epidemiologists and molecular/cellular neuroscientists to further this work.

5.4. Windows of vulnerability

Although substantial emphasis has been placed on the second trimester as a period of vulnerability to schizophrenia, this notion was supported by scant evidence, largely from ecologic studies, as well as by evidence of neuronal migration deficits in schizophrenia (Akbarian et al., 1993). As reviewed above, more recent data, particularly those from cohorts with prospectively acquired data, have suggested that environmental insults acting at multiple points in the life course, from conception to adolescence, may act to elevate risk of the disorder. It appears increasingly likely that such events interact with specific neurodevelopmental processes that occur during restricted intervals of maturation. Congenital rubella and other in utero infections provide an excellent example of this concept. Exposure of a child or adult to rubella has little if any detrimental effect, other than a rash or other mild, self-limited symptoms; however, fetal exposure to rubella is related to severe congenital malformations, including deafness, cataracts, mental retardation, and, as noted above schizophrenia spectrum disorders (South and Sever, 1985). The risk of developing these sequelae is greatest for first trimester exposure and gradually declines as pregnancy progresses. Gestation is a period of remarkable transformation in the fetus, and the fetal brain undergoes rapid developmental changes, from neurogenesis, to neuronal

migration, and differentiation, the formation of neural circuits and networks, and, in later pregnancy, rapid expansion of brain volume (Tau and Peterson, 2010). Synaptic pruning occurs during different periods of life, from the prenatal period to infancy and early childhood, and resumes between childhood and adolescence. Later adolescence is a period of extensive myelination of certain brain structures, including the dorsolateral prefrontal cortex (Benes, 1989). Hence, although much attention regarding the effects of timing of insults on brain development has focused on pregnancy, it is likely that environmental risk factors, such as cannabis use during adolescence, alters critical events that are specifically associated with that developmental period with particular effects on molecular, cellular, and neural network functions that lead to disruptions of neuroanatomy and physiology, thereby increasing the vulnerability to the onset of psychotic symptoms.

To address this question, it will be essential to identify environmental exposure data in which the timing of occurrence has been well documented. In most cases, prospectively collected data are essential. This does not necessarily require a new prospective cohort study, however, given the availability of retrospectively collected data and samples from historical cohorts containing information on the time period during which these resources were obtained.

5.5. Developmental trajectories

The study of developmental trajectories requires novel approaches in the research design, data collection, and analysis. A longitudinal design with data collected at frequent intervals prior to illness onset is ideal. Although the statistical approaches to analysis of trajectory data is still under development, a variety of methods have been proposed and utilized. The most effective approaches operate under the premise that both normal and deviant trajectories operate nonlinearly (James and Silverman, 2005).

The benefits of trajectory analyses to the study of schizophrenia may be far-reaching. Data that are properly obtained and analyzed could yield essential information necessary to take preventive measures long before onset of the illness. Prodromal studies of schizophrenia, in which individuals with attenuated psychotic symptoms or genetic liability are identified, offer much promise, and, for example, a recent study suggests that administration of docosahexaenoic acid could delay or prevent the progression of psychotic symptoms (Amminger et al., 2010); however, it is possible that by the time these individuals have already manifested these symptoms and presented for treatment, some or most of the brain pathology may not be reversible. Conceivably, if extensive knowledge were available not only on the trajectory of a developmental event, but also on well-documented environmental risk factors, family history of psychiatric disorder, and genetic polymorphisms, this may create the potential for developing a sufficiently sensitive and specific index of risk that could be applied for prediction of schizophrenia and for early intervention.

6. Conclusions

In recent years, we have witnessed an accumulation of evidence suggesting that environmental factors play a significant role in the etiopathogenesis of schizophrenia. Epidemiologic studies of these risk factors have evolved over the years from the use of ecologic and non-systematically collected data to sophisticated research designs including longitudinal cohorts. Collectively, these studies suggest that a diversity of factors, including in utero infections, micronutrient deficiency, and fetal hypoxia, play a role in the etiology of this disorder. These factors likely interact in complex ways with the macrostructural environment, including the psychological, social, cultural, and economic context to increase risk of schizophrenia. Based on findings from other areas of medicine, and early results from studies of schizophrenia, it appears increasingly likely that a large portion, if not the

majority of schizophrenia cases can be accounted for by interactions between environmental and genetic factors and by other mechanisms involving the subtle interplay between environments and genes. With a few notable exceptions, studies conducted to date that are focused on environmental factors largely exclude genotyping, and investigations of genetic variants largely exclude measurement of the environment. One approach to address this limitation is to leverage new methods which integrate environmental and genetic influences.

Additional challenges faced by the field of environmental epidemiology involve the timing during which exposures are measured, several types of biases, confounding, and a lack of studies of other psychiatric outcomes. These limitations restrict the extent to which causal inferences can be drawn and may have contributed to both negative as well as possible spurious findings.

Fortunately, new birth cohort studies offer the potential to remedy these limitations and move the field forward in important ways. These cohorts offer the advantages of large sample sizes, prospectively collected data, centralized registries on obstetric experience and on schizophrenia and other psychiatric outcomes. In some cohorts, archived biological specimens are available for analysis of environmental biomarkers that were not measured during the pregnancies and DNA were acquired. This provides the capability to replicate previous associations and to explore novel environmental agents from a wide variety of domains. These studies also may allow for testing mediating and moderating factors including childhood developmental trajectories and other environmental exposures.

This work may ultimately have important implications for public health strategies aimed at the prevention of schizophrenia given that many environmental risk factors can be addressed with existing interventions and treatments, many of which are inexpensive and can be scaled up to cover large populations. These studies also offer the promise of identifying pathogenic mechanisms that act to derail the ontogeny of critical neurodevelopmental events. The use of developmental animal models, such as maternal immune activation, that reflect actual environmental insults may complement existing animal models which are based on pharmacologic and genetic manipulations. In our view, these approaches offer great promise in elucidating the etiopathogenesis of schizophrenia.

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Abbreviations

BMI	body mass index
CB₁	cannabinoid receptor 1
CHDS	Child Health and Development Study
CMV	cytomegalovirus
CNS	central nervous system
CNVs	copy number variants
COMT	catechol-O-methyl transferase
CPP	Collaborative Perinatal Project
CRH	corticotrophin-releasing hormone

SGA	small for gestational age
C-Section	Cesarean-section
CSP	cavum septum pellucidum
d-ALA	delta-aminolevulinic acid
DIBS	Developmental Insult and Brain Anomaly in Schizophrenia Study
DNLS	Danish National Longitudinal Study
DNMT1	DNA methyltransferase 1
DOPAC	3,4-dihydroxylphenylacetic acid
FiPS	Finnish Prenatal Studies
GABA	gamma-aminobutyric-acid
GAD67	glutamic acid decarboxylase
GR	glucocorticoid receptor
GSH	glutathione
GWAS	genome wide association studies
HSV	Herpes Simplex Virus
HVA	homovanillic acid
JPS	Jerusalem Perinatal Study
KPMCP	Kaiser Permanente Medical Care Plan
LPS	lipopolysaccharide
MAP-2	microtubule associated protein-2
MHC	major histocompatibility
MIA	maternal immune activation
MRI	magnetic resonance imaging
MTHFR	methylenetetrahydrofolate reductase
MZ	monozygotic twins
NK	natural killer
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
nNOS	neuronal nitric oxide synthase
OCs	obstetric complications
PAP	population attributable proportion
poly I:C	polyinosinic:polycytidylic acid
PPD	prenatal protein deprivation
PPI	pre-pulse inhibition
RBDEP	Rubella Birth Defects Evaluation Project
Rh	Rhesus

ROS	reactive oxygen species
SAM	S-adenosyl-methionine
TNF-α	tumor necrosis factor- α
WHO	World Health Organization.

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Fig. 1. Developmental trajectory following prenatal exposure to rubella. ^aLimbic hyperdopaminergia, prefrontal hypodopaminergia, and decreased NMDA have not been shown to be affected by in utero rubella.

Table 1

Prenatal nutrition and schizophrenia.

Authors and year	Location	Type of study	N	Diagnosis	Finding
Susser and Lin (1992)	Netherlands	Retrospective cohort analysis with ecologic data on exposure	35 exposed cases	ICD-9 diagnoses for schizophrenia determined through Dutch psychiatric registry	Birth cohorts exposed to severe food deprivation during the Dutch Hunger Winter of 1944/1945 during the 1st trimester showed a two-fold increase in hospitalized schizophrenia for women but not for men
Susser et al. (1996)	Netherlands	Retrospective cohort analysis with ecologic data on exposure	9656 exposed cases	ICD-9 diagnoses for schizophrenia determined through Dutch psychiatric registry	Exposure to famine during the Dutch Hunger Winter of 1944/1945 in early gestation was associated with a twofold and statistically significant increase in the risk for schizophrenia in both men and women
Hoek et al. (1996)	Netherlands	Retrospective cohort analysis with ecologic data on exposure	156 cases	ICD-6 and ICD-9 diagnosis for schizoid personality disorder obtained from military induction data	Males exposed to severe famine during Dutch Hunger Winter of 1944/45 in early gestation had a 2.7-fold increase in the risk of schizophrenia spectrum disorder (schizophrenia plus schizophrenia spectrum personality disorder)
Schaefer et al. (2000)	Alameda County, California	Birth cohort study and analysis	63 cases	DSM-IV schizophrenia spectrum disorders (SSD), including schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorder NOS, and schizotypal personality disorder, diagnosed through psychiatric record review and diagnostic interview (Diagnostic Interview for Genetic Studies)	High compared with average maternal pre-pregnant BMI (kg/m ²) was associated with a nearly three-fold significantly increased risk for SSD in adult offspring
Wahlbeck et al. (2001)	Helsinki, Finland	Birth cohort study and analysis	114 cases	DSM-III-R diagnoses of schizophrenia and schizoaffective disorder determined from data from Finnish Hospital Discharge Register	Mothers' late-pregnancy BMI of 30 associated with 1.09 per kg/m increase in risk of schizophrenia in offspring
Kawai et al. (2004)	Hamamatsu City, Japan	Cohort analysis	52 cases	DSM-IV diagnoses of schizophrenia in in- and outpatients from University Hospital	A one-unit increase of BMI in early pregnancy and a 19% increase in late pregnancy were associated with a 24% increase in risk of schizophrenia
St Clair et al. (2005)	Wuhu region of Anhui, China	Retrospective cohort analysis with ecologic data on exposure	4597 cases	Diagnoses from inpatient and outpatient psychiatric case record review from Fourth People's Hospital of Wuhu, 1971–2001. Schizophrenia defined by ICD-8 and 9	Subjects born during 1959–1961 Chinese famine years had a two-fold increase in rate of schizophrenia, not accompanied by a change in proportion of familial cases; results suggested that early gestational exposure conferred the increased risk
Brown et al. (2007)	Alameda County, California	Nested case-control study	63 cases	Schizophrenia spectrum disorders (SSD), including schizophrenia, schizoaffective disorder, delusional disorder, psychotic	Elevated 3rd trimester homocysteine (related to low folate levels) associated with a greater than two-fold statistically significant increase in risk of SSD

Authors and year	Location	Type of study	N	Diagnosis	Finding
Insel et al. (2008)	Alameda County, California	Prospective birth cohort	57 cases	disorder NOS, and schizotypal personality disorder, diagnosed through psychiatric record review and diagnostic interview (Diagnostic Interview for Genetic Studies) DSM-IV diagnoses of schizophrenia spectrum disorders (SSD), including schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorder NOS, and schizotypal personality disorder, diagnosed through diagnostic interview (Diagnostic Interview for Genetic Studies) and psychiatric record review	A mean maternal hemoglobin concentration of 10.0g/dL or less was associated with a nearly four-fold statistically significant increased rate of SSDs compared with a mean maternal hemoglobin concentration of 12.0 g/dL or higher, adjusting for maternal education and ethnicity. For every 1-g/dL increase in mean maternal hemoglobin concentration, a 27% decrease in the rate of SSDs was observed
Xu et al. (2009)	Liuzhou prefecture of Guangxi autonomous region in China	Retrospective cohort analysis of ecological data	4974 cases	Chinese Classification of Mental Disorders (CCMD) and ICD-10 diagnoses of schizophrenia determined by chart review	Subjects conceived or in early gestation at the height of 1959–1961 Chinese famine had a two-fold increased risk of schizophrenia with risk related to severity of famine conditions
McGrath et al. (2009)	Denmark	Nested case-control study	424 cases	Schizophrenia ICD-10 from psychiatric register	Subjects in the lowest 3 quintiles and highest quintile had a two-fold increased risk of schizophrenia compared with subjects in the fourth quintile

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Table 2

Rh and other blood incompatibility and schizophrenia.,

Authors and year	Location	Type of study	N	Diagnosis	Finding
Hollister et al. (1996)	Denmark	Birth cohort study	21 male cases	ICD-8 diagnoses of schizophrenia determined through National Psychiatric Register	Rh incompatibility associated with a 2.78-fold increased risk of schizophrenia in male offspring. The risk was present only in second or later born offspring
Palmer et al. (2002)	Finland	Family-based candidate-gene study	181 cases	DSM-IV diagnoses of schizophrenia, schizoaffective disorder, or schizophrenia spectrum disorder (i.e., paranoid personality, schizoid personality, and schizotypy) determined by record review.	Incompatibility between maternal and fetal genotypes was associated with a 2.6-fold increased risk of schizophrenia
Insel et al. (2005)	Alameda County, California	Birth cohort study and analysis	71 cases	ICD-9 and DSM-IV diagnoses of schizophrenia spectrum disorders (SSD), including schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorder NOS, and schizotypal personality disorder, diagnosed through diagnostic interview (Diagnostic Interview for Genetic Studies) and record review	Rh incompatible offspring had a 1.8-fold, though nonsignificant, increase in risk of schizophrenia; a significant sex by exposure interaction was observed, with a greater increase in male offspring. A modest increase in risk of schizophrenia was also observed for ABO incompatibility (involving a mother with blood type O and offspring with either A or B blood types), and a significant interaction effect was demonstrated between the sex and exposure

Table 3

Prenatal stress and schizophrenia.

Authors and year	Location	Type of study	N	Diagnosis	Finding
Huttunen and Niskanen (1978)	Helsinki, Finland	Retrospective population-based cohort study	167 cases	Psychiatric disorders including: schizophrenic psychoses, manic-depressive psychoses, minor depressive and neurotic disorders, alcoholism and/or personality disorders, social behavior, childhood behavior disorders determined through review of psychiatric registry	Loss of father during months 3–5 and 9–10 of pregnancy associated with increased risk of psychiatric disorders in offspring
Myhrman et al. (1996)	Northern Finland	Birth cohort study	76 cases	DSM-III-R diagnosis of schizophrenia determined through psychiatric record review	Unwanted pregnancy was associated with a greater than two-fold statistically significant increase in schizophrenia risk in the offspring
van Os and Selten (1998)	Netherlands	Retrospective birth cohort study	1899 cases	Diagnosis of schizophrenia identified through National Psychiatric Case Register	Prenatal exposure to the May 1940 five-day invasion of the Netherlands by the German forces was associated with increased incidence of schizophrenia, especially in those exposed in the 1st trimester (1.28-fold increase in risk) and in men (1.35-fold increase in risk)
Selten et al. (1999)	Netherlands	Retrospective epidemiological study	118 cases	ICD categories schizophrenic disorder, paranoid state and other non-organic, non-affective psychosis identified through Dutch Psychiatric Register	Prenatal exposure to 1953 Dutch Flood Disaster was associated with 1.8-fold increase in risk of non-affective psychosis, but the association was not significant
Herman et al. (2006)	Alameda County, California	Prospectively collected birth cohort analysis	71 cases	Schizophrenia Spectrum Disorders (SSDs), including schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorder NOS, and schizotypal personality disorder, diagnosed through psychiatric record review and diagnostic interview (Diagnostic Interview for Genetic Studies)	Unwantedness of pregnancy was associated with a 1.75-fold increase in risk for adult schizophrenia spectrum disorders but the effect was non-significant
Khashan et al. (2008)	Denmark	National population-based study	7331 cases	ICD-8 and ICD-10 diagnoses of schizophrenia and related disorders determined from Danish Psychiatric Central Register	Offspring whose mothers were exposed to death of a relative, or who had a relative diagnosed with cancer, acute myocardial infarction, or stroke syndrome during the 1st trimester had a 1.67-fold increased risk of developing schizophrenia and related disorders

Table 4

Adolescent cannabis use and schizophrenia.

Authors and year	Location	Type of study	N	Diagnosis	Finding
Andreasson et al. (1987)	Sweden	Historical cohort study of Swedish military conscripts from 1969	246	ICD-8 Diagnosis of schizophrenia and other psychoses determined by psychiatric interview	High cannabis consumption (use on more than 50 occasions) at conscription (age 18) had a six-fold increase in risk of schizophrenia after 15-year follow-up compared with nonusers
Arseneault et al. (2002)	Dunedin, New Zealand	Prospective longitudinal birth cohort study	759	DSM-IV Diagnoses of schizophrenia and depression and diagnoses of schizophrenia disorder and depression determined with a standardized interview	Subjects who used cannabis by age 15 were four times more likely to have a diagnosis of schizophreniform disorder at age 26 than controls. After psychotic symptoms at age 11 were controlled for, risk for adult schizophreniform disorder remained higher among those who used cannabis at age 15; however, this risk was no longer significant
Zammit et al. (2002)	Sweden	Retrospective cohort study of Swedish conscripts from 1969	362 cases	ICD-8 diagnoses of schizophrenia and other psychoses determined by record linkage	Use of cannabis in adolescence was associated with increase in risk of developing schizophrenia in a dose dependent fashion both for subjects who had ever used cannabis and for subjects who had used only cannabis and no other drugs. Subjects who had ever used cannabis had only a 1.2-fold increase in risk, while subjects who used cannabis > 50 times had a 6.7-fold increase in risk
Fergusson et al. (2003)	Christchurch, New Zealand	Prospective longitudinal birth cohort study	1011 subjects assessed at both age 18 and 21	Psychotic symptoms assessed in an interview using the Symptom Checklist 90 (SCL-90)	Cannabis dependence disorder at age 18 associated with a two-fold increased risk of psychotic symptoms at age 21, even after adjustment for prior psychotic symptoms
Caspi et al. (2005)	Dunedin, New Zealand	Prospective longitudinal birth cohort study	36 cases	DSM-IV diagnosis of schizophreniform disorder determined with a standardized interview	A functional variation in the catechol-O-methyltransferase (COMT) gene increased the effect of adolescent cannabis use on risk of adult psychosis
Henquet et al. (2005)	Germany	Prospective data analysis from a population based sample	2437 total subjects	Symptoms of psychosis determined by psychiatric interview	Cannabis use at baseline increased the cumulative incidence of psychotic symptoms by 1.7-fold after adjustment for age, sex, socioeconomic status, urbanicity, childhood trauma, predisposition for psychosis at baseline, and use of other drugs, tobacco, and alcohol. The effect of cannabis use was stronger in those with any predisposition for psychosis at baseline than in those without. The risk difference in the "predisposition" group was significantly greater than the risk difference in the "no predisposition" group. Predisposition for psychosis at baseline did not significantly predict cannabis use four years later

Table 5

Comparison of effect sizes between biomarker/clinically derived maternal risk factors and susceptibility genes for schizophrenia.

Environmental exposures	Effect size ^a	Susceptibility genes (SNPs)	Effect size ^a
Influenza 1st half of pregnancy	3.0	Neuregulin (NRG1)	0.90–1.27
Toxoplasmosis high (1:128–1:1024)	2.6	DISC 1	0.77–1.46
Genital/reproductive periconception	5.3	Dysbindin	0.14–2.01
Respiratory infection 2nd trimester	2.1	COMT	0.76–1.49
HSV-2	1.51–1.6	DAOA (G72)	0.71–1.26
Hemoglobin	1.60–3.73	RGS4	0.78–1.22
Homocysteine	2.39		
Lead (d-ALA)	1.58–2.43		

^aOdds ratios are provided for influenza, toxoplasmosis, herpes simplex virus, homocysteine, lead, and for all of the susceptibility genes (SNPs). Rate ratios are provided for hemoglobin and genital/reproductive infection.