INTRODUCTION

Schizophrenia is a globally pervasive neuropsychiatric disorder with an approximate prevalence of 1% in any given adult population (Lauriello, Bustillo, & Keith, 2005) and a mean annual incidence rate of 0.2 per 1000 with a range of 0.04–0.58 per 1000 people (Eaton, 1999). In terms of incidence across countries, a study conducted by the World Health Organization has found contrasting results. In studies of narrowly defined schizophrenia, the incidence rate did not differ significantly across societies, but when schizophrenia was more broadly defined, the highest incident rates occurred in developing countries compared to industrialized countries (Jablensky et al., 1992). In addition, this study found a higher incidence of catatonic schizophrenia in developing countries.

Schizophrenia is characterized by cognitive, behavioral, and emotional abnormalities, including positive symptoms (e.g., delusions, hallucinations, catatonic behavior, disorganized speech) and negative symptoms (e.g., alogia, affective flattening, amotivation) (Buchanan & Carpenter, 2005). Furthermore, chronically disturbed cognition has been observed in several domains such as executive function, attention, and verbal fluency and causes considerable impairment in level of functioning (Gold & Green, 2005). Although research on the etiologies of this neuropsychiatric disorder is still in an early phase, the general consensus is that environmental risk factors, susceptibility genes, and their interaction lead to the eventual development of schizophrenia, and that much of the liability to schizophrenia is initiated by insults that occur during different windows of brain development, from the prenatal period up to adolescence. The neurodevelopmental hypothesis of schizophrenia suggests that these insults are most detrimental during certain critical periods of vulnerability (Piper et al., 2012). These insults’ origins are believed to alter the neurodevelopmental trajectory of specific neurotransmitters and other molecules, synapses, cells, brain regions, and neural circuits and networks, leading to pathophysiologic and neuromorphologic alterations and ultimately behavioral outcomes characteristic of the disorder.

In this chapter, we review findings of specific environmental factors that have been found to contribute to schizophrenia. We will primarily focus on environmental insults that play a significant role during the prenatal and childhood phases of life, examining in particular infection, nutrition, cannabis use, advanced paternal age, immigration, and childhood trauma. We will then consider the diathesis-stress model in which genetic and environmental factors interact to influence the development of schizophrenia. Finally, we offer potential recommendations and interventions that are feasible at present which might help to prevent or mitigate the severity of schizophrenia and discuss future directions for research in this area of work.

EVIDENCE FOR ENVIRONMENTAL FACTORS IN SCHIZOPHRENIA

Schizophrenia is a heritable disorder. Early research on schizophrenia was dominated by twin, family, and adoption studies (Lowing, Mirsky, & Pereira, 1983; Reiss, 1976; Tienari et al., 1987). More recently, linkage and genome-wide association studies have identified chromosomal regions and genetic variants, both inherited and de novo, which are related to an increased risk of the disorder (Fromer et al., 2014).
Despite the importance that genetics has on the development of schizophrenia, environmental risk factors have emerged as potentially important in the etiology of this disorder. Twin studies have found a concordance rate of approximately 50–60% in monozygotic (MZ) twins, which falls well short of complete concordance (McGuffin, Owen, & Farmer, 1995). Furthermore, this concordance rate is skewed by the fact that MZ twins generally share a similar in utero environment as well as greater similarities in the postnatal environment.

In a study that examined the difference in concordance rates within only MZ twins, Davis, Phelps, and Bracha (1995) found that there was a difference in these rates when comparing monochorionic and dichorionic MZ twins, the latter of whom have separate placentae and fetal circulation. In monochorionic MZ twins, who share a greater in utero environment almost from conception, the concordance rate of schizophrenia is 60%, whereas it is only 11% in dichorionic twins. Hence, this study supports an environmental role in the development of schizophrenia, even within MZ twin pairs.

Next we discuss major environmental risk factors that have been identified to date for schizophrenia and the evidence supporting their relationship with the disorder.

Prenatal Infection

A role of prenatal infection in schizophrenia is supported by several lines of research. Initial studies have found an increased risk of schizophrenia in children born during the winter and spring months, potentially reflective of respiratory infections in particular, and birth in urban settings, where infections can spread more rapidly (for a review, see Brown & Derkits, 2010).

More recent studies have focused on birth cohorts comprising children all born within the same time period and in which records of maternal infection, psychiatric illnesses, and related records were maintained throughout the pregnancy and during the early life of the child. These allow for long-term assessment to the diagnosis of schizophrenia; comparison of psychiatric and other outcomes among subjects with prospectively documented infection with those considered to be free of infection. Some cohorts capitalize on biological samples from the pregnancy and the fetus that were also stored. These samples have been used to serologically confirm antibodies to infection.

Next we review results of select studies of specific prenatal infections and schizophrenia (for a review, see Brown and Derkits, 2010).

Influenza

Because influenza is so prominent during the winter and the spring months, investigators began to examine the psychiatric outcomes of children born during influenza epidemics (Brown & Derkits, 2010). In the earliest studies, some were able to find a link between being born during an influenza epidemic and developing schizophrenia during adulthood, whereas others failed to replicate these results. These studies were limited in that it was possible that a significant proportion of the mothers did not have influenza at the time of pregnancy because individuals in these studies were included merely because they were pregnant during the time of the influenza exposure rather than being confirmed with influenza during pregnancy.

Therefore, researchers used birth cohort studies to document maternal influenza exposure during the pregnancy by relying on documented records and biomarkers prospectively collected during pregnancy. These subjects were linked to registries that contained data on psychiatric outcome. In some studies, the patients were interviewed, whereas in others, the registry diagnoses were used. One such study was conducted by Brown et al. (2004) using the birth cohort of the Child Health and Development Study, born between 1959 and 1967 in Alameda County, California, and followed by the Kaiser Foundation Health Plan. Strengths of this study included documentation and availability of maternal serum drawn during the pregnancy, psychiatric diagnoses based on structured interviews and reviews of psychiatric records of the offspring, and regular follow-up of the cohort. Quantification of influenza antibody in these specimens led to the finding that among mothers who were exposed to influenza during the first half of gestation, there was a threefold elevation in the risk of developing schizophrenia. If the exposure occurred during the first trimester of pregnancy, the risk was increased sevenfold. However, if the exposure to influenza was in the second half of gestation, there was no increased risk for schizophrenia.

These results correspond with those that have emerged from an increasing number of animal studies, including those on rodents and rhesus monkeys, of influenza and of maternal immune activation. These studies demonstrated that both of these immunologic exposures, particularly during early-to-middle gestation, were related to neurobiological and behavioral outcomes that are analogous to those found in schizophrenia or related psychoses (Bauman et al., 2014; Meyer, Yee, & Feldon, 2007; Vuillermot, Webber, Feldon, & Meyer, 2010).

Rubella

Researchers have also tested the risk of schizophrenia in a birth cohort exposed to the rubella virus. Rubella was one of the first known teratogens, with a spectrum of effects on congenital development including mental retardation, deafness, and cataracts as well as a 20% risk of miscarriage (Siegel, Fuerst, & Guinee, 1971). These findings suggested that rubella might also lead to
long-term developmental consequences, such as schizophrenia, that may not be immediately apparent at birth.

Brown et al. (2001) investigated a birth cohort in which pregnant women were diagnosed as having had prenatal exposure to the rubella virus by clinical signs and confirmatory serological testing. In a longitudinal follow-up of the infants in this cohort, the authors found that more than 20% of the exposed children later developed schizophrenia or schizophrenia spectrum disorders. Much like the results found for influenza, the correlation was strongest when mothers were exposed to rubella during the first 2 months of pregnancy.

One hypothesis for how rubella affects the developing fetus is by altering the neurodevelopmental trajectory of the child, as this study found that approximately 90% of the rubella-exposed children who eventually developed schizophrenia spectrum disorders had increased neuromotor and/or behavioral abnormalities during childhood as well as a decline in intelligence quotient over time. This finding was in contrast to a much smaller proportion of these childhood neurodevelopmental abnormalities in those whose mothers were exposed to rubella during pregnancy, but who did not eventually develop these disorders.

**Herpes Simplex Virus Type 2**

Another viral infection with detrimental effects on infants is herpes simplex virus type 2 (HSV-2), a sexually transmitted virus which is transmitted to the infant from the mother as the fetus passes through the birth canal. Similar to rubella, HSV-2 causes abnormal neurological development and other related developmental consequences (Whitley, 2006).

One study that has examined the link between maternal HSV-2 infection and schizophrenia in offspring was by Buka, Tsuang, Torrey, Klebanoff, Bernstein, et al. (2001). Elevated levels of maternal immunoglobulin G (IgG) antibody associated with HSV-2 were linked to a higher risk of psychosis in those mothers’ offspring. A larger follow-up study by Buka, Cannon, Torrey, and Yolken (2008) again found a higher risk of psychosis and an even higher risk of schizophrenia-related psychosis in offspring whose mothers tested positive for exposure to HSV-2 during pregnancy. This risk was particularly elevated in mothers who engaged in risky sexual practices during pregnancy, such as frequent sexual encounters without contraception. This was a particular strength of the study (Brown & Derkits, 2010).

**Cytokines and Other Inflammatory Biomarkers**

Cytokines, which encompass a family of soluble polypeptides, represent markers of prenatal infection and inflammatory conditions. Cytokines orchestrate the immune response to the presence of infections and other noxious insults and therefore play an essential role as part of the immune system. Hence, cytokine elevations may indicate exposure to a number of different types of infections during pregnancy.

In examining the connection between elevated levels of maternal cytokines and the development of schizophrenia in the offspring, Brown, Hooton, et al. (2005) found a twofold increase in levels of the pro-inflammatory cytokine interleukin-8 during the second and early third trimesters of pregnancies of offspring who later developed schizophrenia compared with control pregnancies. A second study by Buka, Tsuang, Torrey, Klebanoff, Wagner, et al. (2001) found that the mothers of children who developed psychosis later in life had higher levels of the pro-inflammatory cytokine tumor necrosis factor-α at the time of birth. Elevated cytokine levels have also been associated with other conditions such as a higher body mass index (BMI) (Schaefer et al., 2000) and preeclampsia (Cannon, Jones, & Murray, 2002), both of which have also been associated with schizophrenia (Brown, Michaeline, & Susser, 2005). Hence, cytokine levels may not necessarily indicate maternal prenatal infection, but can be an important indicator of other insults to the fetus and newborn. In the most recent study of a prenatal inflammatory biomarker and schizophrenia, Canetta et al. (2014) demonstrated that elevated maternal C-reactive protein measured during pregnancy in archived serum specimens is associated with an increased risk of schizophrenia in offspring from a Finnish national birth cohort.

**Toxoplasma gondii**

Nonviral or bacterial infections also have detrimental effects on fetal development. *Toxoplasma gondii* is an intracellular parasite that can increase the risk of schizophrenia in infants whose mothers were exposed to this pathogen during pregnancy (Brown, Schaefer, et al., 2005). Levels of *T. gondii* IgG antibody in archived maternal sera were greater than twice as high in mothers of children who developed schizophrenia compared with mothers of control offspring. *Toxoplasma gondii* has also been linked to congenital central nervous system (CNS) abnormalities and delays in neurological development, which supports its biological plausibility for increasing the risk for schizophrenia (Dukes, Luft, Durack, Scheld, & Whitley, 1997).

In a second study, which used *T. gondii* IgG antibody measurements on filter paper blood spots collected from newborns (first week of life), Mortensen et al. (2007) found that *T. gondii* IgG levels were higher in those who later developed schizophrenia compared with controls. This antibody most likely originated from the mother rather than the child, because the antibody crosses the placenta and *T. gondii* infection is highly unlikely in the first week of life. A more recent study of IgG levels measured in neonatal dried blood
spots by Blomstrom et al. (2012) again associated higher levels of T. gondii IgG with later schizophrenia. These findings support the original results of Brown, Schaefer, et al. (2005).

**Maternal Infection and the Pathobiology of Schizophrenia**

Evidence from our group indicates that prenatal infection can have pathobiological consequences that are observed in schizophrenia, including effects on neurocognition. A study by Brown et al. (2009) investigated the relationship in schizophrenia patients between having had prenatal exposure to influenza or toxoplasmosis and subsequent performance on neurocognitive measures, including the Wisconsin Card Sorting Test and the Trail Making Test, part B. Schizophrenia patients who were exposed to maternal infection during gestation committed significantly more errors on the Wisconsin Card Sorting Test and needed significantly more time to complete the Trail Making Test, part B test. Furthermore, the patients showed deficient abilities on figural fluency, sequencing of letters and numbers, and backwards digit span, suggesting that prenatal infection may affect cognitive abilities, specifically set-shifting function, and that there may be associated abnormal physiological changes in the brain.

A study by Ellman et al. (2012) linked mothers who had anemia to an increased deficiency in neuromotor functions and intellectual difficulties in schizophrenia patients but not in controls. Schizophrenia offspring of mothers with lower hemoglobin values throughout pregnancy had a significant decrease in scores on the Grooved Pegboard test, the Finger Tapping test, and the Wechsler Adult Intelligent Scales. These results suggest that having a liability to schizophrenia make offspring more vulnerable to the negative cognitive effects of decreased maternal hemoglobin values.

**Prenatal Nutrition**

Deficient prenatal nutrition has also been implicated as a leading candidate risk factor in the etiology of schizophrenia. Some of the first studies on the effects of prenatal nutrition on the later development of schizophrenia were conducted on individuals who were born or in gestation during the Dutch Hunger Winter of 1944–1945 (Hoek, Brown, & Susser, 1997). This was a severe famine resulting from a blockade of the Netherlands by the Nazi regime. This led to thousands of deaths as well as deceased fertility and infant mortality. Because the caloric content of the rations and psychiatric outcomes were well documented and the famine was considered relatively time-limited, this was an opportunity to study the effects of prenatal nutrition on a cohort that was exposed to nutritional deficiency during specific periods of gestation.

This series of studies reported that the timing of the exposure may determine the type of psychiatric disorder that eventually develops, and that exposure to famine and malnutrition earlier in gestation may lead to more severe psychiatric disorders including schizophrenia and schizoid personality disorder (Hoek et al., 1997; Susser et al., 1996). Specifically, these studies found an increased risk of schizophrenia and schizophrenia spectrum disorders, as well as schizoid personality disorder, among those exposed to the peak of the famine during conception and early gestation. The authors of the study suggest that these findings might be explained by direct effects of protein caloric malnutrition, by micronutrient deficiency, or an unknown cooccurring factor. In a related study, Brown, van Os, Driessen, Hoek, and Susser (2000) demonstrated that the risk of developing unipolar or bipolar major affective disorder requiring hospitalization was higher in the subjects exposed to this famine during the second trimester and highest in those exposed during the third trimester. This study not only supports the earlier findings that prenatal malnutrition can have severe effects on psychiatric disorders, but also suggests that the timing of exposure to malnutrition may modify the type of psychiatric disorder that results.

The authors also found that early gestational exposure to the Dutch famine was associated with congenital abnormalities of the CNS, which is concordant with earlier work on this cohort and with the finding that exposure to famine during this period was also related to an increased risk of schizophrenia. Specifically, researchers found an increased rate of neural tube defects among the children who were in gestation during the famine. Interestingly, neural tube defects are related to prenatal folate deficiency, which is common during pregnancy, suggesting that this micronutrient may be a viable candidate risk factor for schizophrenia. Other nutrients related to neural tube defects and the folate metabolic cascade are vitamins B12 and B6. The lack of folate and of these vitamins causes maternal hyperhomocysteinemia (Penner & Brown, 2007). In the birth cohort of the Child Health and Development Study, we found a significant elevation in maternal homocysteine during pregnancy in cases of schizophrenia compared with matched controls (Brown et al., 2007). Elevated homocysteine levels may lead to an increased risk of schizophrenia by interfering with the development of N-methyl-D-aspartate receptors and leading to glutamatergic deficits (Picker & Coyle, 2005).

Low levels of prenatal vitamin D in the pregnant mother have also been associated with schizophrenia (McGrath, Eyles, & Mowry, 2003). Although prenatal vitamin D deficiency can be caused by maternal malnutrition, it is also related to seasonal fluctuations resulting in daily length of light exposure or migration to geographical regions with colder climates and less sunlight. Insufficient levels of vitamin D have been found in
animal models to correspond to biological abnormalities seen in schizophrenia, and it is hypothesized that lack of vitamin D affects cell growth and proliferation and alters the immune system response in both the developing fetus as well as in adult brain.

Iron is another important nutrient that is essential for brain development and functioning. Prenatal iron deficiency or a lack of iron in the early stages of life may lead to permanent neurological and behavioral abnormalities from childhood, extending into adulthood. A study by Insel, Schaefer, McKeague, Susser, and Brown (2008) investigated the effect of maternal iron deficiency on the relative risk of developing schizophrenia or schizophrenia spectrum disorders during adulthood in the Child Health and Development Study birth cohort. The authors found that low maternal hemoglobin (in the anemic range), a robust marker of iron that was prospectively documented in all members of the cohort, was associated with a nearly fourfold increased risk of schizophrenia spectrum disorders in their offspring, adjusting for many covariates.

In an attempt to replicate the findings of this study, Sorensen, Nielsen, Pedersen, and Mortensen (2011) examined a cohort of Danish births from 1978 to 1998. The authors found that the individuals whose mothers had been diagnosed with anemia during pregnancy had a 1.60-fold increased risk for developing schizophrenia. Further research is required to identify plausible mechanisms by which prenatal iron deficiency modulates the risk of schizophrenia. Finally, new research has found that maternal iron deficiency may interact with prenatal infection and immune activation to contribute to schizophrenia-like behavior in rat offspring (Harvey & Boksa, 2014).

Additional nutritional risk factors for schizophrenia include maternal vitamin A deficiency (Bao et al., 2012) and excess docosahexaenoic acid (Harper et al., 2011).

McClellan, Susser, and King (2006) have suggested that lack of proper prenatal nutrition could lead to de novo mutations in the genes responsible for promoting healthy brain development. A developing fetus requires proper nutrients, as they are responsible for protecting, synthesizing, and repairing DNA (Ames, 2001). An excess of mutations in the genes that are critical to brain development could result in impairments in both brain structure and function. The timing of origin of these mutations is also essential because the fetus is most vulnerable during early gestation from the high cell division rate at this time; mutations that appear during or around the time of conception can lead to an exponential growth of mutant cells (Paashuis-Lew & Heddle, 1998).

Malnutrition could also lead to epigenetic changes in genes responsible for proper fetal development. Notably, folate is a known methylator of genes, because gene methylation generally represses gene expression (Yu et al., 2014), its absence may act to increase gene expression. The consequences may depend upon the gestational time period of exposure. For example, in a study by Heijmans et al. (2008), infants who were in gestation during the Dutch Hunger Winter displayed epigenetic changes in the insulin-like growth factor 2 gene compared with same-sex siblings who were unexposed during gestation. These and other epigenetic differences could be a mediator between prenatal malnutrition and the expression of genes related not only to fetal growth, but also neuropsychiatric development.

Prenatal and perinatal malnutrition may also modify fetal brain development through physiologic mechanisms that are implicated in schizophrenia. As an example, maternal iron deficiency is known to diminish myelination (Wu et al., 2008), and animal, postmortem, and neuroimaging studies support myelin deficits in schizophrenia (Flynn et al., 2003; Zhang et al., 2012).

Another finding related to prenatal nutrition and schizophrenia is the association between high maternal BMI and schizophrenia among offspring. In this study, conducted on the Child Health and Development Study birth cohort, mothers with a BMI greater than 30 were three times as likely to give birth to offspring who later developed schizophrenia (Schaefer et al., 2000). Furthermore, Solomon et al. (1997) found that gestational diabetes is correlated with high BMI as well as with the obstetric complications seen among infants who later develop schizophrenia. In addition, elevated BMI is associated with increased inflammation (Kitahara et al., 2014), which has also been associated with schizophrenia (Canetta et al., 2014). Hence, high BMI may lead to obstetric complications (Crane, Wojtowycz, Dye, Aubry, & Artal, 1997), or inflammation, which then increase the risk of the development of schizophrenia in the offspring (Cannon et al., 2002). This work has particularly important implications for public health as the obesity epidemic has become an increasing problem in industrialized countries (Güngör, 2014).

Paternal Age

Advanced paternal age has been identified as a risk factor for schizophrenia. In a seminal study, Malaspina et al. (2001) reported this finding on a single large birth cohort in Israel, the Jerusalem Perinatal Cohort. The authors found that advanced paternal age was correlated with the risk of schizophrenia beginning as early as 25 years of age. The risk of schizophrenia increased rapidly as paternal age advanced, with a relative risk of 2 in offspring of men who were 45–49 years old at time of birth of the child and nearly 3 in offspring of men older than 50. Advanced maternal age was not associated with schizophrenia and the paternal age finding persisted following adjustment for maternal age. In addition, the finding persisted after accounting for length of marriage
as well as family history of schizophrenia and other psychiatric illnesses. The finding has been replicated by many groups throughout the world (Brown et al., 2002; Dalman & Allebeck, 2002; El-Saadi et al., 2004; Tsuchiya et al., 2005).

This finding has been hypothesized to result from de novo genetic mutations that are highly correlated with older paternal age (Kong et al., 2012; Malaspina et al., 2001). Unlike ova, spermatogonia undergo an exponentially rising number of cell divisions as paternal age increases. After a male experiences puberty, spermatogonia experience approximately 23 divisions per year, leading to about 200 divisions by age 20 and 660 by age 40 (Malaspina et al., 2001). This rapidly increasing number of cell divisions as paternal age advances, accompanied by deficits in DNA repair mechanisms, may be at least partially responsible for the increase in de novo mutations. Indeed, many studies have identified a significant excess of copy number variants in schizophrenia, including de novo mutations, and several are associated with very high risks of the disorder (Rippey et al., 2013; Merikangas et al., 2014; Luo et al., 2014). In an Icelandic cohort of fathers and offspring, Kong et al. (2012) found that the age of the father at conception of the offspring was the driving force behind the diversity in mutation rate of single nucleotide polymorphisms, with paternally derived mutations doubling every 16.5 years. Furthermore, they found that the father’s age explained nearly all of the de novo mutations remaining after accounting for random variation.

An excess of de novo mutations would at least partially explain why schizophrenia persists in the population despite a reduction in reproductive fitness in this disorder. Parenthetically, inherited genetic variants for schizophrenia are expected to have been subject to negative selection pressures. Consequently, it has been argued that if new genes for schizophrenia were not introduced, the disorder should have either disappeared, or become rarer over time.

Cannabis Use

Cannabis, a drug prepared from the plant Cannabis sativa (including marijuana, resin, and ‘skunk’), is used widely throughout the world and is especially popular in North America, Western Europe, West and Central Africa, and Oceania (United Nations Office on Drugs and Crime, 2009). Several studies within the past decade have investigated the effect of continuous use of cannabis on psychotic illnesses, specifically schizophrenia. Zammit, Allebeck, Andreasson, Lundberg, and Lewis (2002) in Sweden found that those who smoked cannabis had a twofold increased risk of developing schizophrenia within 15 years. In addition, the researchers also found a dose–response relationship; subjects who used cannabis more heavily (over 50 reported occasions) were six times as likely to develop schizophrenia compared to those who did not use cannabis at all.

Subsequent studies were carried out in different countries, which confirmed the results found in the Zammit et al. (2002) study, showing that those clinically dependent on cannabis by 18 years of age had an increased risk of later developing psychotic symptoms (Fergusson, Horwood, & Swain-Campbell, 2003). Cannabis users were also more likely to develop schizophreniform disorder (Arseneault et al., 2002), and the dose–response relationship found in the first study was confirmed (Henquet et al., 2005).

Experimental studies have also been conducted in order to assess the effect of cannabis use on schizophrenia. D’Souza et al. (2004) administered varying levels of the main ingredient in cannabis to healthy individuals with a history of cannabis exposure (but not abuse) and found that the subjects in the study displayed both positive and negative symptoms associated with schizophrenia, although all symptoms disappeared by about 3 h. D’Souza et al. (2005) conducted a follow-up study in which they followed the same protocol, but with clinically stable schizophrenia patients. Again, they found brief increases in positive symptoms, even if the patients were already taking antipsychotics.

More recent studies have focused on the mechanisms behind the schizophrenia–cannabis interaction. Epstein and Kumra (2014) tested the effect of cannabis on executive control of attention and cognitive function by comparing scores on the Attention Network Test among people with early-onset schizophrenia (EOS) and cannabis use disorder, only EOS, only cannabis use disorder, and controls. They found that the first group in particular had less efficient executive control of attention compared with those who had only EOS. They also found a smaller right caudal anterior cingulate cortex in subjects with EOS and cannabis use disorder. However, it is presently unclear whether this means that the smaller cortex surface leads to deficits in self-regulation and heavy cannabis use or if the direction of causation is in the opposite direction. More recent studies have suggested gene–environment correlation between cannabis use and schizophrenia in that the increased risk of schizophrenia after heavy and consistent cannabis use may be moderated by a shared gene that may explain part of the association (Power et al., 2014).

In support of the previous study by Power et al. (in press), a second study by Giordano, Ohlsoo, Sundquist, Sundquist, and Kendler (2015) found that the relationship between cannabis use or abuse and schizophrenia may not be as strong as believed. The authors found that as the degree of shared genetic and environmental
factors increased (beginning with first cousins to full siblings), the relationship between schizophrenia and cannabis abuse decreased, although it remained significant even in full sibling pairs.

Immigration Status

First- and second-generation migrants have a higher risk of schizophrenia (Selten, Cantor-Graae, & Kahn, 2007). This idea was originally presented in a paper by Odegaard (1932), who found that Norwegian immigrants in the United States were more likely to be admitted to the hospital for schizophrenia compared with Norwegians born in the United States or those who still lived in Norway. Cantor-Graae and Selten (2005) followed up on this idea, finding a higher incidence of schizophrenia among subjects in the United Kingdom who originally had an African Caribbean background; individuals in the Netherlands with a Surinamese, Dutch Antillean, or Moroccan background; and subjects of various ethnic backgrounds in Denmark. In addition, subjects who immigrated from a developing country were more likely to develop schizophrenia than those from a developed country.

In the 2007 paper, Selten et al. reaffirmed this finding from the 2005 meta-analysis (Cantor-Graae & Selten, 2005). The authors found a relative risk for schizophrenia of 2.7 among first-generation migrants and a relative risk of 4.5 among second-generation migrants. They found an especially high risk of schizophrenia for migrants in Europe from countries with high black populations; this finding was replicated in further studies (Dealberto, 2010). Dealberto (2010) suggested that vitamin D deficiency in dark-skinned individuals might be responsible for this higher rate of schizophrenia. Cantor-Graae and Selten (2005) proposed an alternative explanation for their findings, namely the experience of social defeat, which they define as a subordinate position in society or an outsider status. The authors suggested that the chronic experience of social defeat through high competition in jobs, housing, and other aspects of life leads to increased sensitivity in the mesolimbic dopamine system. In support of this theory, the authors observed that immigrant groups who suffer from a low socioeconomic status in a highly competitive atmosphere have the highest risks for schizophrenia, although this association may be due to social selection rather than social causation. In addition, people with dark skin often have to endure higher levels of racism and ethnic discrimination. Further proposed explanations or contributing factors involve an ethnic disadvantage in the immigrants’ new home countries, an increase risk of schizophrenia in those living in urban settings, unemployment, poor housing conditions, and general social adversity.

Birthplace and Residence

The risk of schizophrenia is influenced by the place of birth and childhood residence, specifically in urban versus rural locations. Studies have consistently shown that being raised in an urban setting leads to a higher risk of developing schizophrenia and that this risk is related to the level of urbanicity in a dose–response relationship (March et al., 2008). In addition, a large study by Mortensen et al. (1999) found that birth in an urban setting is related to schizophrenia risk, with a twofold increased risk in those born in the capital of Denmark compared with those born in the rural regions. Pedersen and Mortensen (2001) also found that the timing of exposure to urban settings was related to schizophrenia, but that being raised in an urban setting was a greater risk factor than being born in an urban area. Further evidence indicated that family-level and individual-level exposure to urbanicity were important in the relationship between degree of urbanization and the development of schizophrenia (Pedersen & Mortensen, 2006). Finally, a recent study by Sariaslan et al. (2015) found that population density as measured when the subject was 15 years of age was a predictor of later schizophrenia.

However, in a more recent meta-analysis of four studies by Vassos, Pedersen, Murray, Collier, and Lewis (2012), including the 1999 study by Mortensen et al., the authors found that the timing of exposure to urbanicity in an individual’s life did not change the relationship with schizophrenia. Potential explanations included individual or family characteristics, selective migration, a greater risk of being exposed to infections or pollutants, an insufficient diet, or a poor social environment. In addition, the authors point to social fragmentation and deprivation as a possible explanation.

Socioeconomic Status

Two different hypotheses have been generated and tested to account for the relationship between low socioeconomic status and schizophrenia (Dohrenwend et al., 1992). The first is social causation, which proposes that schizophrenia is due to the environmental disadvantages that people with a low socioeconomic must endure. An alternative hypothesis, social drift, argues that individuals with schizophrenia tend to move from higher to lower socioeconomic status because of the debilitating symptoms that accompany the illness. A full discussion of this question has been well covered in other references (Dohrenwend et al., 1992; Kwok, in press) and will therefore be only briefly discussed here.

Studies have found conflicting evidence, ranging from no link between socioeconomic status and schizophrenia (Hare, Price, & Slater, 1972; Timms, 1998) to the finding that those with schizophrenia are more likely to
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Examined records of hospital psychosis, the risk was much higher. In a second study, on a group of children raised by adoptive parents, adoptees whose nonbiological families were disadvantaged, measured by unemployment, living in apartments, or a single-parent household, had an increased risk for psychosis resulting from social adversity. Several indicators of low socioeconomic status during childhood were related to a greater risk for psychosis and schizophrenia, including rented apartments, single-parent households, unemployment, and social welfare benefits. The risks increased with the number of indicators present; individuals with four indicators of low social status had a 2.7-fold higher risk of schizophrenia compared with individuals who did not have any. In a second study, on a group of children raised by adoptive parents, adoptees whose nonbiological families were disadvantaged, measured by unemployment, living in apartments, or a single-parent household, had an increased risk for psychosis. Among those who also had a genetic liability for psychosis, the risk was much higher.

Childhood Abuse

Morgan and Fisher (2007), in a review of several studies, reported that subjects with psychotic disorders were more likely to have experienced childhood trauma. Although the work was important, the reviewed studies had certain limitations. The authors did not control for the various kinds of abuse (e.g., physical, sexual, psychological) and the studies generally had small numbers of subjects. Moreover, only a small number of studies examined subjects who were children or adolescents at that time, and there was a mixture of inpatient and outpatient samples of which there was only a minority with a diagnosis of psychosis. In addition, the studies that investigated subjects with a diagnosis of psychosis did not always focus specifically on schizophrenia. Finally, there were variations between studies in how childhood trauma was defined and measured, and studies did not always account for comorbid disorders and illnesses.

More recent studies have found a link between childhood sexual abuse and schizophrenia as well as positive symptoms in psychotic patients, specifically auditory hallucinations (Sheffield, Williams, Blackford, & Heckers, 2013). Patients with auditory hallucinations had the highest level of abuse, specifically sexual abuse. A second study found that an overwhelming majority of patients with schizophrenia spectrum disorders had experienced at least one stressful or traumatic event in their lifetime, and the group had experienced a median of seven traumatic events (O’Hare, Shen, & Sherrer, 2013). Although this study examined schizophrenia specifically rather than psychotic symptoms in general, it did not distinguish abuse from other types of traumatic events.

Despite these initial findings, however, Spataro, Mulvaney, Burgess, Wells, and Moss (2004) noted that positive symptoms, including hallucinations, can be seen in cases of posttraumatic stress disorder, and for individuals who have experienced any kind of child abuse, schizophrenia symptoms may be confounded with symptoms of posttraumatic stress disorder, which can be a comorbid diagnosis. Therefore, although child abuse may be a risk factor for schizophrenia, there may not be a causal connection between them.

INFECTIONS AFTER BIRTH

In addition to the large body of evidence suggesting that prenatal infections give rise to an increased risk of schizophrenia, some mixed evidence has suggested a link between certain infections in those who already have developed schizophrenia (Yolken & Torrey, 2008). Torrey, Bartko, Lun, and Yolken (2007) found a twofold increased risk of schizophrenia in those with T. gondii infections; these findings have been replicated by some other groups. The direction of causation, however, is unclear. One study that attempted to address this, by Niebuhr et al. (2008), found that toxoplasma IgG antibodies in archived serum specimens of the US military drawn within 6 months of diagnosis were associated with a modest increase in risk of schizophrenia, although this relationship was not found in serum drawn before the 6 months leading up to diagnosis.

Amminger et al. (2007) found that subjects with more severe positive psychotic symptoms (although without a diagnosis of schizophrenia) were more likely to be seropositive for toxoplasma IgG, and the more severe the symptoms, the higher the level of IgG antibody. Finally, cytomegalovirus has been investigated as a possible risk factor for schizophrenia postnatally, but there have been mixed results (for a review, see Brown & Derkits, 2010).

Dalman et al. (2008) examined records of hospital admissions for CNS infections in children between birth and 12 years of age for nonaffective psychiatric illnesses from 14 years of age onwards for all the children born within a cohort in Sweden. These infections were further divided into bacterial versus viral infections and then divided more specifically into named illnesses such as the mumps virus and cytomegalovirus. A slightly higher risk for both nonaffective psychotic illnesses and schizophrenia was found to be associated with viral CNS infections, specifically the mumps virus and cytomegalovirus, but not with bacterial infection.

Some studies have examined whether antibiotic or antiviral medications that treat cytomegalovirus or T. gondii improve the severity of psychotic symptoms (Dickerson, Boronow, Stallings, Origoni, & Yolken, 2003; Dickerson, Stallings, Boronow, Origoni, & Yolken, 2009).
These two studies have produced positive and negative results, respectively. One possible reason for these conflicting findings is that the neuropathology may have been treated too late to be reversible with antibiotics.

**GENE–ENVIRONMENT INTERACTION**

It is unlikely that the environmental exposures reviewed here act alone to cause psychopathology. Rather, many investigators have proposed integrative, or diathesis–stress models, that incorporate genetic influences, including interactions between genetic mutations and environmental factors. According to this model, by interacting with genetic influences, these environmental factors impact development of the brain during critical periods and trigger the onset of psychotic syndromes such as schizophrenia (Brown, 2011; Brown & Derkits, 2010; van Os, Kenis, & Rutten, 2010). Various environmental influences act on sensitive subgroups of the population with a genetic predisposition to such environmental effects (van Os, Rutten, & Poulton, 2008).

This vulnerability is especially salient during critical periods of neuronal and brain development (Arnsten, 2009). Furthermore, repeated exposure to these insults has been associated with more severe psychotic symptoms, especially in those who experienced adversity early in life who become more sensitive to environmental stress in adulthood, possibly from altered dopamine activity in the brain (Glaser, van Os, Portegijs, & Myin-Germeys, 2006).

One example of a gene–environment interaction is provided by a potential relationship between the genes that encode the major histocompatibility complex class I proteins, which have been associated with schizophrenia in genome-wide association studies (Walters et al., 2013) and prenatal infection (McAllister, 2014). These proteins are necessary for proper functioning of not only T lymphocytes, but also synaptic function. It has been suggested that individuals with these mutations are more sensitive to the effects of a prenatal infection or other environmental events that activate the immune system (Brown & Derkits, 2010). According to this hypothesis, this aberrant immune response subsequently leads to a greater degree of modification of major histocompatibility complex class I function, leading to abnormal synaptic function, which is abnormal in schizophrenia (Stephan, Baldeweg, & Friston, 2006). In this way, major histocompatibility complex molecules might be one of many mediators between genetic and environmental contributions to schizophrenia.

Recent work by Kannan, Sawa, and Pletnikov (2013) on mouse models of gene–environment interaction has supported the diathesis-stress model. The authors found an interaction between psychological stress and the Disrupted-in-Schizophrenia-1, a genetic candidate for schizophrenia, in producing neurochemical and behavioral deficits. Other studies have found interaction effects between specific genes and stressors such as immune activation (Vuillermot et al., 2012) and cannabis use (Behan et al., 2012). In a recent study of interaction between environmental events, Giovanoli et al. (2013) demonstrated that exposure in mice to prenatal infection, combined with trauma during peripuberty, leads to pathological effects on behavior and neurochemistry during adulthood.

**Intervention and Prevention**

One of the key implications of research on environmental factors in schizophrenia is a potential role in prevention. Primary prevention includes interventions that attempt to reduce the incidence of schizophrenia by providing feasible interventions either to the general public (“universal prevention”) or to specifically targeted populations (Gordon, 1983; Mrazek & Haggerty, 1994). Secondary prevention aims to avert serious symptomatology by means of early intervention at the first stage of pathology. Tertiary prevention aims to provide the most efficient treatment and rehabilitation to subjects already diagnosed with the disorder to prevent future relapse.

One metric used to assess the potential impact of a preventive approach is the population attributable risk, which is an estimate of the number of cases of a disease that could be prevented in a population if a certain risk factor was completely eliminated from that population (Brown & McGrath, 2010). Related to the population attributable risk is the number needed to prevent. This is a measure of the number of people from whom a specific risk factor would need to be removed to prevent a single new case of a disease.

Another factor that is used in decisions on prevention and intervention is risk assessment. The Global Burden of Disease project uses risk assessment to comparatively examine disorders to ascertain which have the greatest public impact. This allows policy makers to decide upon appropriate allocations of funding for proper treatment and prevention of different disorders (Murray & Lopez, 1996), taking public safety and known risks of the intervention or research into account.

At least some prenatal infections are preventable. We had found that the population attributable risk for exposure to influenza, *T. gondii*, and genital infections was about 30% (Brown & Derkits, 2010), meaning that if each of these infections were entirely eliminated from the pregnant population that we studied, nearly one-third of cases of schizophrenia could be eliminated. Although it is not feasible to entirely eliminate these infections and the findings were calculated only from estimates from
our cohort studies, and thus may vary by population, this suggests that preventive efforts may lead to a sizable reduction in the incidence of schizophrenia. With regard to influenza, vaccination is readily available in developed countries and continually updated to reflect new strains that come into existence every year. Maternal influenza is a potential risk factor not only for schizophrenia in the offspring, but also for other abnormal outcomes of the pregnancy, such as bipolar disorder (see the discussion in the next section) as well as fetal mortality (Zaman et al., 2008). Therefore, pregnant women have been identified as a population that should be targeted for influenza vaccination (Centers for Disease Control and Prevention [CDC], 2013). We have also argued that women planning a pregnancy and/or of reproductive age should consider influenza vaccination (Brown & Derkits, 2010). Furthermore, it might be prudent to increase efforts for influenza vaccination among the wider population to control the spread of the virus to pregnant women and to newborn infants.

Toxoplasma gondii is also preventable. Most individuals become infected with this parasite by ingesting oocyst-infected soil or water, eating contaminated food that is undercooked, or lacking proper hygienic measures when changing cat litter boxes (Elmore et al., 2010). Therefore, by using safety precautions such as handwashing after contact with soil, using gloves when changing cat litter boxes as well as thorough cooking practices, the incidence of T. gondii may be reduced in the population. Furthermore, all of these recommendations can be implemented with little or no cost.

Genital and reproductive infections, which are usually sexually transmitted infections may be difficult to control in the population, but general education about the risks of unsafe sex and use of condoms reduce the frequency of new cases of sexually transmitted infections in communities (Vivancos, Abubakar, Phillips-Howard, & Hunter, 2013). Furthermore, a vaccine has been developed for a specific sexually transmitted infection called human papillomavirus; universally vaccinating children against human papillomavirus may prevent patients from developing as they grow older and become sexually active (Deleré et al., 2014). Furthermore, prompt and proper treatment of those already infected with sexually transmitted infections may reduce the impact of the infection or cure it completely, should treatment be timely enough.

Prevention of prenatal malnutrition may be more challenging than preventing certain prenatal infections, given that protein-calorie malnutrition is commonly caused by social adversity or factors that require great effort to control. However, micronutrient deficiencies in the pregnant population are more readily preventable through improved obstetric counseling, education, and preventive interventions. For example, considerable proportions of the pregnant population do not receive adequate quantities of vitamins such as folic acid (Ray, Singh, & Burrows, 2004) or vitamin D (Bodnar et al., 2007), deficiencies of which have been implicated in schizophrenia (see the discussion in the prenatal malnutrition section) and that can be eliminated by taking prenatal vitamins.

Finally, risk factors such as cannabis use are widespread and difficult to control; indeed, some US states are beginning to overturn these laws and marijuana is legal in many other countries (Palamar, Ompad, & Petkova, 2014). One potential avenue of intervention might involve counseling on the effects of cannabis use among individuals with a family history of schizophrenia.

### FUTURE DIRECTIONS

We suggest several directions for future work in this area. First, in addition to replicating previous associations, a significant priority should be given to the identification of new environmental exposures that may be involved in the pathogenesis of schizophrenia. Translational research on animal models as well as emerging work in clinical neuroscience will have an important role to play in this regard in that this work is expected to identify novel candidates for testing in epidemiologic studies. A second key issue is to use this work for the identification of common pathophysiologic pathways. As an example, we and other groups aim to examine how effects of prenatal infections are mediated through inflammatory pathways such as cytokines and C-reactive protein. Third, it will be key to study developmental trajectories, as revealed by several approaches including neurocognitive testing and neuroimaging. This will allow for relating risk factors identified from epidemiologic studies with pathobiologic processes in schizophrenia. Fourth, this work has significant future implications for genetics and epigenetics. Regarding genetics, we expect that future work will allow for the discovery of interactions between environmental exposures and susceptibility genes, or allow for the identification of new susceptibility genes by studying subjects with a common environmental exposure that plays a causal role. A related avenue of exploration is epigenetics: As discussed previously, it is likely that environmental exposures exert their influences via effects on the epigenome, and this may be one mechanism by which gene–environment interactions operate. Fifth, as discussed previously, this work could have significant potential for future public health interventions aimed at prevention of the environmental exposures and may help to stimulate responsible agencies, including those of governmental and nongovernmental organizations to develop feasible prevention strategies. Sixth, it will be critical to assess whether the...
environmental exposures that are related to schizophrenia may be risk factors for other psychiatric disorders. Our group has demonstrated, for example, that maternal influenza may be a risk factor for bipolar disorder with psychotic features among offspring (Canetta et al., 2014) and that elevated maternal C-reactive protein is a risk factor for both autism (Brown et al., 2014) and for schizophrenia (Canetta et al., 2014).

CONCLUSION

Epidemiologic studies of schizophrenia have revealed increasing evidence that environmental factors at key periods of life increase vulnerability to the disorder. These factors include infection, malnutrition, cannabis use, and social factors such as migration, childhood trauma, and socioeconomic status. These effects have been supported by an expanding literature on these same risks in animal models and by new research on the clinical pathobiology of schizophrenia. Although still in its infancy, it is likely that interactions between genetic and environmental, and between different environmental exposures, account for a considerable risk of the disorder. Implications of these studies include preventive approaches, and offer suggestions for future research that may capitalize on emerging findings from translational research.

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