Prenatal Factors in Schizophrenia

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Abstract
The purpose of this review is to summarize the current state of knowledge on how nongenetic factors occurring before, during, or soon after birth are related to schizophrenia. Schizophrenia is a complex psychiatric illness with a varied clinical presentation that has both environmental and genetic origins and that may result from insults to the nervous system that occur throughout development. In line with this, several endogenous (internal) and exogenous (external) nongenetic factors of pregnancy and birth have been related to an increased risk for schizophrenia in later life. These factors include maternal diabetes, low birth weight, older paternal age, winter birth, and prenatal maternal stress, among others. Although each of these nongenetic factors alone slightly increases the risk for schizophrenia, risk increases when these factors combine with each other and with other risk factors. The mechanisms that link each specific risk factor with the occurrence of schizophrenia remain largely unknown. In order to build better models of the illness, researchers will have to address the question of how environmental and genetic risk factors work together in increasing risk and explore to what extent certain underlying risk factors may explain different aspects of the disease.

Keywords
neurodevelopment, schizophrenia, risk factors, obstetric complications, prenatal maternal stress

Schizophrenia is a complex psychiatric disorder affecting approximately 1% of the population. Much of the variability in neurobiology, childhood adjustment, symptom profile, onset, course, treatment response, and long-term outcome may well be explained by variability in causes of schizophrenia. There is a clear genetic component to schizophrenia, but despite decades of research, the “schizophrenia gene” remains elusive (Nöthen, Nieratschker, Cichon, & Rietschel, 2010). Some researchers have therefore suggested that schizophrenia may arise from alterations in how some genes are “turned on or off” due to exposure to nongenetic (or environmental) factors (Rutten & Mill, 2009). Exposure to certain environmental factors could also contribute to spontaneous genetic mutations that give rise to vulnerability for the illness. Strong support for the role of environmental factors in the etiology of schizophrenia comes from the finding that in identical twin pairs, in which the twins share about 100% of their DNA, if one twin develops schizophrenia the other twin has only a 50:50 chance of developing it.

Neurodevelopmental models of schizophrenia (Murray, 1994) suggest that schizophrenia results from some combination of genetic and/or environmental insults to the developing nervous system. Some of these insults may occur before birth, lying dormant until later life when normal changes in the brain should occur. Physical markers for which the prenatal developmental processes are known and that are seen more frequently in individuals with schizophrenia than in community controls (e.g., minor physical anomalies and asymmetric fingerprints) suggest that an insult occurring at a particular time in gestation could affect neurodevelopment and leave behind these physical clues. “Static” neurodevelopmental models implicate events occurring prenatally or perinatally (i.e., around the time of birth), while “progressive” neurodevelopmental models include insults that may occur until the final stages of brain development are complete early in a person’s twenties (Woods, 1998)—insults such as childhood maltreatment, head trauma, or adolescent cannabis use. Genetic and environmental risk factors may combine in additive or multiplicative ways to increase an individual’s risk to a point beyond some threshold for illness (Malaspina, Sohler, & Susser, 1999).

Here, we describe those environmental factors occurring during pregnancy and birth that are associated with increased risk for schizophrenia. We make a distinction, albeit imperfect, between endogenous (internal) factors that have their origins within the mother’s body, the uterus, and the fetus, and exogenous factors with external origins.
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Endogenous factors

Pregnancy and birth complications. The risk of developing schizophrenia is increased approximately twofold (thus, to 2%) in individuals who were exposed to various complications during pregnancy (Cannon, Jones, & Murray, 2002). There are three major categories of complications: (a) complications of pregnancy, (b) abnormal fetal growth and development, and (c) delivery complications. Many of these obstetric complications may compromise neurodevelopment.

In a meta-analysis (combining the results of studies that address the same research question), several obstetric factors were associated with risk for schizophrenia (Cannon et al., 2002). During pregnancy, preeclampsia (i.e., hypertension), bleeding, and diabetes have been most consistently associated with schizophrenia (Cannon et al., 2002). Preeclampsia and bleeding might lead to deficient supply of oxygen to the fetus and may impair the developing nervous system. However, how exactly maternal diabetes influences the fetal brain is unknown.

Of the factors that are related to growth and development of the fetus, low birth weight of the child has been most consistently linked to schizophrenia, with birth weight below 2000 grams increasing schizophrenia risk nearly four times (Cannon et al., 2002). However, low birth weight is often due to prior adverse influences on the fetus, whether of environmental or genetic origin.

The complications of delivery that appear to be linked to schizophrenia are asphyxia (i.e., severely deficient supply of oxygen), uterine atony (i.e., loss of tone in the uterine musculature), and emergency caesarean section (Cannon et al., 2002). Some researchers have proposed that complications of delivery might be the consequence of prior abnormalities in the fetus, but findings that neurological abnormalities were even lower in fetuses with more complications of delivery contradicted this hypothesis (McNeil & Cantor-Graae, 1999).

Parental age. Parental age, specifically the biological father’s age, has also been found to be associated with schizophrenia. The results of a recent meta-analysis (Wohl & Gorwood, 2007) suggest that late fatherhood increases a child’s risk of developing schizophrenia, with the risk increasing approximately from 0.2% in children of 35-year-old fathers to 5% in children of 55-year-old fathers. This may be explained by the number of mutations in a man’s germ cell (sperm) that increase throughout the life span. These cells will have undergone about 660 divisions by the age of 40. In contrast, female germ cells (eggs) only divide 24 times, mostly before a woman is even born. Every division increases the risk of new mutations, and such mutations have been implicated in various genetic (i.e., autosomal dominant) diseases such as Huntington’s disease and dwarfism.

Exogenous factors

Season of birth. First reported in 1929, winter birth is one of the most firmly established nongenetic risk factors for schizophrenia. Compared to the monthly birth rates in the general population, there is a 5% to 8% excess of births in winter and early spring months in those who later develop schizophrenia (Torrey, Miller, Rawlings, & Yolken, 1997). The season-of-birth effect has been observed in the northern hemisphere and, although less consistently, in the southern hemisphere; no season-of-birth effect has been found in equatorial regions where there is little variation in seasonal temperatures. Studies conducted in the northern hemisphere have generally reported an excess of births among individuals with schizophrenia for the months of December through March, with a maximum peak in January and February.

Researchers are still trying to understand how season of birth might increase risk for developing schizophrenia. There may be seasonal patterns of procreation in the parents of individuals with schizophrenia. Exposure to seasonally fluctuating factors that could potentially interfere with the development of the central nervous system in utero has also been suggested as a mechanism—factors including nutrition, hormones, maternal exposure to viral infections, and certain meteorological factors (e.g., sunlight exposure and vitamin D, temperature, or severe weather; Tochigi, Okazaki, Kato, & Sasaki, 2004).

Maternal infections. Much research suggests that prenatal maternal infection can increase the risk for schizophrenia (Brown & Derkits, 2010). Initial studies examining the relationship between maternal infectious disease and subsequent schizophrenia were epidemiological in nature, linking influenza epidemics to increases in population levels of schizophrenia, for example. Given the limitations of this methodology (i.e., no validation of maternal exposure), researchers have since relied on other sources of information such as maternal recall, hospital records, and national registry records of documented infection. However, the strongest line of evidence comes from studies with maternal exposure to infection that has been documented serologically (i.e., from blood samples). These studies suggest there is an increased risk for schizophrenia in people prenatally exposed to toxoplasmosis (2.6-fold increase), influenza (3-fold increase), or genital or reproductive infection (5-fold increase; Brown & Derkits, 2010).

It is hypothesized that maternal infection in the early to midstages of pregnancy damages the developing nervous system of the fetus, which subsequently leads to the development of schizophrenia. Proposed mechanisms include the direct effects of the pathogen on the fetal brain, maternal immune reaction to infection, fever, stress, and use of analgesics and anti-inflammatory drugs (Boksa, 2008).

Urbanicity and toxins. The prenatal infection hypothesis gains support by the finding that birth in an urban area is associated with a 2.4-fold increased risk of schizophrenia.
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(Tandon, Keshavan, & Nasrallah, 2008). This effect may be due to crowding in urban areas and the subsequent increase in risk for infection, although this remains a topic of debate. In a similar vein, urbanicity may be associated with an increased exposure to toxic substances (e.g., lead). Current findings suggest that elevated prenatal levels of lead are in turn associated with an almost twofold increase in the risk of schizophrenia and related disorders (Opler & Susser, 2005).

**Nutritional factors.** Maternal nutrition in pregnancy is also believed to influence risk for schizophrenia in offspring (Brown & Susser, 2008). Support comes from two epidemiological studies that found a twofold increase in risk for schizophrenia among individuals who were in their first trimester of gestation at the height of a severe, sudden-onset famine. Additionally, some studies have reported that high maternal prepregnancy and early pregnancy body mass index (BMI) is associated with a 2.8-fold increase in risk for schizophrenia in offspring (e.g., Schaefer et al., 2000). Thus, both under- and overeating during pregnancy may increase schizophrenia risk in the offspring.

There are several hypothesized mechanisms by which maternal nutritional factors may increase the risk for schizophrenia. Regarding maternal undernutrition, it has been suggested that nutritional insufficiencies (e.g., folic acid, essential fatty acids, iron, vitamin A) increase the risk of spontaneous genetic mutations and/or disrupt proper neurodevelopment, ultimately resulting in schizophrenia. The effects of high maternal BMI on schizophrenia risk may be explained by metabolic problems (e.g., diabetes), dietary restrictions, or poor maternal care, all of which may affect neurodevelopment and/or increase the risk of obstetric complications.

**Prenatal maternal stress.** A few studies show that a stressful event occurring outside of the pregnant woman's control (referred to as an independent life event) can result in increased risk for severe psychopathology for her unborn child in adulthood. The stressors studied to date have ranged from population threats of human origin (e.g., tornadoes), to personal loss (e.g., death or fatal illness), to natural events (e.g., tornados), to personal loss (e.g., death or fatal illness) or from Mother Nature (e.g., ice storms). However, a few studies can make direct links between life events in individual mothers and risk in their children. The first study of prenatal stress and schizophrenia is an example. In Finland, Huttenen and Niskanen (1978) found one case of schizophrenia among 168 individuals whose fathers had died during their first year of life, compared to six cases among 167 people whose fathers died while they were in utero, a significant increase in risk. This and other population studies suggest that exposure to stress in the late first or early second trimesters, or possibly at the very end of pregnancy, increases risk for schizophrenia more than does exposure at other times in the pregnancy. Another example is a study by Khashan et al. (2008), who used population registries in 1.4 million Danes to link birth dates to, on one hand, the dates of life-threatening diagnoses or death in close relatives of pregnant women and, on the other hand, to mental illnesses in their children as recorded in the national psychiatric registry. The researchers concluded that the death of a close relative during the first trimester of pregnancy increases risk for schizophrenia in the child by 67%. Huizink and her colleagues (Huizink, Mulder, & Buitema, 2004) review studies of prenatal maternal stress and risk for schizophrenia and other mental illnesses and describe the physiological mechanisms responsible for “schizophrenia-like” effects in animals.

Exogenous sources of stress ultimately have endogenous mechanisms. Animal studies demonstrate that an externally generated stressor to the pregnant female—such as loud noise, social isolation, or pain—results in a surge of stress hormones passing through the placenta to the fetus (Beydoun & Saftlas, 2008). These changes in maternal hormones result in permanent changes to parts of the fetal brain that are associated with schizophrenia (e.g., the hippocampus). Prenatal stress and its effects on the brain are then associated with a number of behaviors in the offspring, including altered stress reactions and learning. Maternal nutritional factors and maternal and fetal immune function may also be important mechanisms of prenatal stress.

The mechanisms of prenatal stress are difficult to study in humans since researchers cannot randomly assign stressors to pregnant women. The human stress experience involves the objective degree of exposure to the stressor, the individual’s subjective distress, and the hormonal response, with several psychological and social factors complicating the process. Prenatal stress may increase risk for schizophrenia directly, by influencing brain development, or indirectly, by increasing the likelihood of other risk factors such as obstetric complications (Beydoun & Saftlas, 2008).

In an attempt to clarify how the objective, subjective, and hormonal aspects of prenatal stress might increase risk for potential precursors of schizophrenia, such as obstetric complications, behavioral problems, cognitive delays, and physical features, we launched Project Ice Storm (King et al., 2009). In this ongoing study, we recruited pregnant women shortly after a natural disaster in 1998 and continue to follow their offspring prospectively. The results of this study may shed light on the mechanisms by which prenatal stress increases risk for schizophrenia. Thus far, results show that greater severity of the mother’s objective exposure to the stressor (the ice storm), but not greater subjective distress, predicts significantly lower cognitive and language performance of her offspring throughout early childhood. Subjective maternal distress predicts more asymmetrical fingerprints, as are found in people with schizophrenia, in the children whose mothers were exposed to the ice storm in mid-pregnancy, when fingerprints develop. Maternal cortisol (a stress hormone) following the ice storm also predicts fingerprint asymmetry in the children. Thus, each aspect of the stress experience (objective, subjective, and hormonal) is associated with one or more risk factors or precursors of schizophrenia. The timing of the stressor at different points in
Discussion

In this brief overview of prenatal and perinatal risk factors for schizophrenia, we have covered risk factors that seem far removed from the illness, like season of birth and severe weather events, and those with more obvious connections to the developing fetus, like birth complications. One point worth mentioning is that these prenatal risk factors are highly nonspecific—that is, they are associated not only with schizophrenia but with a wide variety of other mental illnesses (Huijzink et al., 2004). For instance, prenatal maternal stress may increase risk for depression, anxiety, or aggression in children and adolescents (Beydoun & Saftlas, 2008); the type of difficulty that arises from prenatal stress may be a function of the genetic “weak link” in the fetus. Another point worth stressing is that most of the risk factors we have discussed explain a small, but significant, increase in risk for schizophrenia. For example, while bleeding in pregnancy raises risk an additional 69% above the 1% to 1.69%, an emergency C-section increases risk 300% and diabetes in pregnancy increases risk 700% (Cannon et al., 2002). However, even a sevenfold (700%) risk above 1% is only 7 in 100 cases of maternal diabetes. Hence, as argued below, moving toward the simultaneous examination of multiple risk factors for schizophrenia may prove to be more helpful in understanding the etiology of schizophrenia.

Increasingly, schizophrenia research is moving away from studying single risk factors toward studies that consider how risk factors work together to increase risk. Because gene-by-environment (GxE) interactions are likely in schizophrenia, environmental and genetic factors studied alone may yield negative results until they are paired with each other (Rutter, Moffitt, & Caspi, 2006). The GxE approach may ultimately show how an environmental factor, when paired with different genes, may result in different forms of psychopathology. For example, van Os and colleagues (2004) concluded that between 20% and 35% of individuals exposed to both an urban birth and a family history of schizophrenia could be ill because of this GxE interaction (van Os, Pedersen, & Mortensen, 2004). As the field of “epigenetics” advances, we may also see how environmental factors change how genes are expressed—or turned on and off—which may be another way that environment and genes interact to increase risk.

Although researchers have been mostly interested in uncovering risk factors for the diagnosis of schizophrenia, little research to date has focused on discovering associations between risk factors and specific signs, symptoms, or other features of schizophrenia. Yet the power of using such an approach should be greater than that of studies predicting the diagnosis (King, Laplante, & Joober, 2005).

In summary, decades of epidemiological research have uncovered a wide variety of prenatal and perinatal risk factors for schizophrenia, most with small effects. Our next challenge is to capitalize on the clues provided by the variability in the causes of schizophrenia and in the patterns of symptoms in people diagnosed with schizophrenia to build better models of the development of this illness.

Recommended Reading

Beydoun, H., & Saftlas, A.F. (2008). (See References). An excellent literature review on prenatal maternal stress and its association with both physical outcomes (including brain development) and health outcomes (including mental health).


Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

References


