# Environmental risk factors for psychosis

*Kimberlie Dean, MBBS, MRCPsych; Robin M. Murray, MD, DSc*

*Genetic factors are clearly important in the etiology of schizophrenia, but the environment in which an individual's genes find expression is also crucial to the development of the illness. In this review of environmental risk factors for schizophrenia, we consider risks operating prenatally and perinatally, during childhood, and then later in life prior to illness onset. Some of these risk factors have been well documented, for example, early hazards causing fetal growth retardation or hypoxia, and hazards nearer the onset of illness like drug abuse and migration. Others are much less certain. The importance of interaction between genetic and environmental risk is, however, undoubtedly important and there is emerging evidence for this from a range of sources. As the etiology of schizophrenia is unraveled, the picture becomes more complex, but also more obviously relevant to the plight of the individual patient.*



*Dialogues Clin Neurosci.* 2005;7:69-80.

**Keywords:** *schizophrenia; environment; risk factor; psychosis; etiology*

**Author affiliations:** Division of Psychological Medicine, Institute of Psychiatry, London, UK

**Address for correspondence:** Dr Kimberlie Dean, PO63, Division of Psychological Medicine, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK (e-mail: k.dean@iop.kcl.ac.uk)

Historically, pioneers of the concept of schizophrenia were more convinced of the evidence for hereditary than environmental causes for the disorder. In considering disease causation, Bleuler wrote "Schizophrenia appears to be independent of external conditions and circumstances."[1] Kraepelin also emphasized the importance of inheritance, but did consider that "… influences injurious to the germ might play a certain part in the origin of dementia praecox"; in particular he proposed childhood inflammation of the brain, head injury, and the emotional consequences of imprisonment as potential environmental risk factors.[2] Since the time of Kraepelin and Bleuler, an increasing number of environmental risk factors have been proposed and investigated. This has followed the realization that genes are necessary, but not generally sufficient, to cause schizophrenia; indeed, concordance rates in monozygotic twins are far from 100%.[3] Of course, the investigation of environmental risk certainly does not negate the importance of genetics. Perhaps the most important modern concept in understanding the etiology of schizophrenia is gene–environment interaction.[4,5] Thus, schizophrenia is an illness in which various environmental risk factors act on a complex set of susceptibility genes.

In this discussion, we consider environmental risk factors that may act through the period from conception to onset of illness. We divide this preillness risk period into early life, childhood, and later life for ease of presentation *(Table I)*. The divisions are somewhat arbitrary and certainly several of the risk factors are thought to act at various points throughout the period.

## Early life environment

The discovery of risk factors acting before and shortly after birth has been central to the neurodevelopmental hypothesis of schizophrenia.[6] The hypothesis proposes that envi-

ronmental risk factors interact with genetic factors during this crucial phase in the formation of the nervous system causing subtle abnormalities, which leave the individual vulnerable to psychosis later in life. Indicators of neurodevelopmental deviance associated with schizophrenia include the presence of developmental abnormalities on structural brain imaging, an excess of minor physical anomalies and neurological signs, and behavioral problems in childhood.[7-9] This evidence has been enhanced by the recognition of environmental risk factors for schizophrenia that act in early life, long before any signs of illness are apparent. These are detailed below and include: obstetric complications, prenatal and postnatal infection, and other factors possibly acting during this crucial period of brain development.

## Obstetric complications

Although "birth trauma" was first proposed as a causative factor for schizophrenia in the 1930s,[10] it took a further three decades for the first case-control studies in adults to emerge. Cannon and coworkers[11] have recently reviewed the historical development of research in this area, and describe the progression from early-high-risk and case-control studies through to the phase of population-based studies, which began in the 1990s and continues today. There were clearly a number of methodological problems associated with the earlier studies and the results were often inconsistent. Cannon and her colleagues conducted a meta-analysis of the population-based studies, which developed in response to concerns about selection and information bias in case-control investigations.[11] They identified eight studies for inclusion in the analysis and found significant associations with schizophrenia for 10 individual complications, which they then grouped into three categories: (i) complications of pregnancy (bleeding, preeclampsia, diabetes, rhesus compatibility); (ii) abnormal fetal growth and development (low birth weight, congenital malformations, small head circumference); and (iii) complications of delivery (asphyxia, uterine atony, emergency cesarean section). The effect sizes found for these associations were relatively small (odds ratio [OR] <2) and it is likely that obstetric complications contribute to the causation of schizophrenia only in combination with other risk factors, particularly susceptibility genes.

The association between obstetric complications and schizophrenia appears stronger in those with an early onset of illness.[12,13] Since obstetric complications are thought to be associated with the neurodevelopmental abnormalities proposed to be causative for schizophrenia, their relationship with such characteristics has been of interest. Some, but not all, studies have demonstrated an association between the presence of structural brain abnormalities on imaging and a history of obstetric complications in samples of subjects with schizophrenia.[14-16] The evidence with regard to the relationship between obstetric complications and neurological abnormalities and minor physical anomalies is even less clear.[17,18]

Furthermore, the biological mechanism underpinning the association between obstetric complications and later development of schizophrenia is not yet fully established. Many have postulated a role for fetal hypoxia. Cannon et al[19] found a linear relationship between the number of hypoxia-causing obstetric complications and early onset of schizophrenia. Presumably, hypoxia interacts with susceptibility genes. In view of the suggestion that most of the current candidate genes for schizophrenia operate on the glutamate system,[20] it is of interest that Fearon et al[21] postulate that the effect of obstetric complications might be mediated by glutaminergic excitotoxic damage. Fearon and other researchers have followed up samples of babies subject to early environmental hazards.[22] Thus, adolescents and adults who were born very preterm or with very low birth weight show many of the same brain abnormalities that are found in schizophrenia, such as lateral ventricular enlargement and decrement in hippocampal volume; the abnormalities in later life are predicted by findings at birth on cranial ultrasound.[23]

| Early life | Childhood | Later life |
|---|---|---|
| • Obstetric complications | • Adverse child rearing | • Drug abuse |
| • Season of birth | • Child abuse | • Migration/ethnicity |
| • Prenatal/postnatal infection | • Head injury | • Urbanization |
| • Maternal malnutrition | | • Social adversity |
| • Maternal stress | | • Life events |

**Table I.** Environmental risk factors that have been proposed for schizophrenia.

## Season of birth and the role of infection

Those born during winter or early spring in the northern hemisphere are more likely to develop schizophrenia in later life than those born at other times of the year.[24,25] A recent systematic review and meta-analysis of northern hemisphere season of birth studies reports a pooled OR of 1.07 (confidence interval [CI] 1.05-1.08) and population attributable risk of 3.3% for the excess of winter/spring births.[26] Many potential mechanisms for the season of birth effect have been postulated, including obstetric complications, variations in light, temperature, nutrition, and seasonal genetic effects.[27] Exposure to infectious agents such as influenza during pregnancy is the best studied of the potential explanations for the association.[28]

Gestational infectious agents, particularly viruses such as rubella, cytomegalovirus, and herpes simplex, are known to be associated with abnormalities in central nervous system (CNS) development and consequent neurological disorder among offspring.[29] Thus, gestational infection is certainly a plausible causal agent for schizophrenia.[30]

A positive relationship has been demonstrated in a number of studies between influenza epidemics such as the pandemic that occurred in 1957 and development of schizophrenia among offspring of mothers pregnant during the period of risk; however, results have not been entirely consistent.[31-35] Furthermore, use of such an ecological design as in these population studies is associated with a number of limitations.[36] Cohort studies, which avoid the problem of the "ecological fallacy," have been attempted, but several have failed to find an association between maternal influenza and schizophrenia.[37,38] Determination of exposure relying on self-report coupled with the rarity of the outcome may have limited the accuracy of such cohort studies.[28]

There have been promising results from animal models, however. Shi et al found that pregnant mice infected with influenza gave birth to offspring who became behaviorally abnormal and concluded that the effect was likely to be largely due to the maternal immune response.[39] In addition to influenza, positive associations have been found between development of schizophrenia and maternal exposure to other infectious agents such as rubella[40] and polio.[41] Stored serum samples taken during pregnancy have begun to be exploited by researchers in order to more clearly define exposure to infection and associated immunological reactions. A surprisingly strong association between maternal antibodies to herpes simplex virus type 2 and later psychosis (OR 5.8; CI 1.7-19.3) was reported by investigators involved in the National Collaborative Perinatal Project.[42] More recently, Brown et al analyzed maternal serum from a cohort pregnant during the 1960s in California.[43] Risk of schizophrenia in the offspring was found to be increased sevenfold for those exposed to influenza during the first trimester of pregnancy.

Postnatal infection may also play a role in the etiology of schizophrenia. Childhood viral CNS infection (up to age 14 years) determined prospectively was found to be associated with adult schizophrenia in the Northern Finland 1966 Birth Cohort, although the effect was thought likely to be modest at a population level.[44] Similarly, childhood meningitis (up to age 4 years) was found to be associated with adult psychosis, but not other psychiatric disorders in a Brazilian sample.[45] *Toxoplasma gondii*, an intracellular parasite, has also been considered to be a putative etiological agent acting both before and after birth to increase risk of psychosis.[46]

## Other possible antenatal environmental risk factors

In utero exposure to noninfectious environmental agents, such as maternal stress,[47] maternal malnutrition,[48] maternal diabetes,[11] smoking,[49] and rhesus incompatibility,[50] has also been considered.

A number of investigations have examined the relationship between experience of a stressful event during pregnancy or maternal stress more generally, and later psychosis. Risk of schizophrenia is claimed to be increased among offspring of mothers who were exposed to sudden widespread disasters while pregnant, such as the German invasion of the Netherlands in 1940[51] and a flood in southwest Holland in 1953.[52] Paternal death during pregnancy was examined as a proxy for maternal stress in a study by Huttunen and Niskanen[53] in 1978. They found a sixfold increase in risk of schizophrenia among those whose fathers had died while they were in utero, compared with those subjects who lost their fathers in infancy. Negative results have also been published indicating that considerable caution must be exercised in drawing conclusions about the role of maternal stress during pregnancy and risk of schizophrenia among offspring.[54,55]

Much evidence has accumulated to link early life nutritional status to adult health, particularly in the area of cardiovascular research.[56] It has been argued that the same may be true for schizophrenia.[57] Increased maternal body mass index (BMI) or childhood BMI and ante-

natal exposure to famine have all been found to be associated with an increased risk of schizophrenia.[58-61] Perhaps the best evidence linking nutrition to risk of schizophrenia comes from the Dutch Hunger Winter studies.[62] Food intake for the Dutch population declined dramatically following a Nazi blockade in the mid-1940s. Members of the birth cohort exposed to this food deprivation during first trimester were found to have higher rates of hospitalized schizophrenia.[63] In addition, subsequent investigation has demonstrated that first trimester exposure to famine in a subsample from the cohort was associated with structural brain abnormalities on magnetic resonance imaging (MRI).[64]

Less is understood, however, about the mechanisms underlying these nutritional associations and whether, for example, micronutrient intake is more important than overall caloric consumption. Vitamin D has recently been postulated as a relevant nutritional factor, with low levels of vitamin D being claimed to be linked to risk of psychosis.[65] In a Finnish birth cohort, McGrath et al found that vitamin D supplementation during the first year of life was protective for adult schizophrenia in males.[66] The same research group also investigated the role of vitamin D using a sample of stored maternal serum, but did not find a convincing link between low maternal levels of vitamin D and subsequent risk for schizophrenia among the offspring.[67] In addition, Ozer et al found that psychosis and rickets were inherited independently in their study of a multigenerational family overloaded with both disorders.[68] Disordered folate metabolism has been suggested as a risk factor for later schizophrenia via effects on neurodevelopment, but again this has been little researched.[69] The role of nutrition in early life on later development of psychosis is clearly an area that warrants further investigation, but is likely to be limited by the difficulties inherent in accurate measurement of nutritional status, and the role of confounding factors.

## Childhood environment

A number of environmental risk factors have been proposed to act during the intermediate period between the prenatal period and life immediately prior to illness onset; these include child-rearing experiences, head injury, and possibly child abuse. The impact of these factors on an understanding of the etiology of schizophrenia has perhaps not been as great as the insights provided by the recognition of earlier and later life risks. In addition, it must be recognized that the environment during childhood is likely to be interacting with the social, behavioral, and cognitive antecedents of psychosis known to predate illness in vulnerable children.[7]

The impact of the child-rearing environment has been highlighted by results from an Israeli study,[70] which examined the role of child rearing by comparing the effects of kibbutz versus family upbringing. The investigators concluded that kibbutz-rearing of high-risk children may increase their risk of developing a psychiatric disorder, though not necessarily schizophrenia. Risk of later schizophrenia has also variously been found to be associated with atypical mother–infant interaction,[71] early parental loss,[72] and poor mothering.[73] In the Dunedin longitudinal birth cohort study, mothers of offspring later diagnosed with schizophreniform disorder were significantly more likely to have atypical mother–child interactions compared to controls (OR 2.65; CI 1.2-5.6).[71] This was not true for mothers of offspring with other psychiatric disorders such as mania, anxiety, or depression.

In those adoptees already at high familial risk of schizophrenia, the quality of adoptive childhood rearing experiences has also been found to be important.[74] In a national Finnish sample, offspring of mothers with schizophrenia given up for adoption had, as expected, significantly higher proportions of both psychoses and other severe mental illness compared with a matched control sample of adoptees. Interestingly though, in this sample, the difference between high and low genetic propensity was only found among those with a disturbed adoptive family environment suggesting a gene–environment interaction.

Some tentative evidence is emerging that not only adverse child-rearing experiences, but also frank child physical or sexual abuse may play a role in increasing future risk of psychosis.[75] In a recent review, Read et al argue that such evidence complements a diathesis-stress model of psychosis and highlights the similarities between biological sequelae of childhood abuse and those associated with schizophrenia.[75] Others have focused on the psychological impact of childhood trauma, which may predispose to later psychotic symptoms via changes in cognitive and affective functioning.[76] Child abuse is certainly not etiologically specific for psychosis,[77] but within psychosis what evidence there is points toward a particular relationship with positive psychotic symptoms.[78] Of course, such symptoms are not necessarily part of schizophrenia and indeed, the association has also been found in a general population sample.[79]

Head injury has been considered as a possible risk factor. Major head injury in adulthood has been associated with a schizophrenia-like clinical picture,[80] but whether the long-term consequences of milder head injury, which is common in childhood, include schizophrenia is less clear. Some retrospective case-control studies have found an association between childhood head injury and later schizophrenia, but results have not been consistent.[81,82] In a sample taken from multiply affected families, those with schizophrenia were more likely to have a history of head injury (OR 2.35; CI 1.03-5.36) compared with their unaffected siblings, again pointing to a gene–environment interaction.[83] Clearly, if the association between childhood head injury and later psychosis is causal, it will only be important in only a small minority of patients.

## Later life environment

While early life risk factors have lent weight to the neurodevelopmental model of schizophrenia, environmental risk factors acting later in life have more often than not encouraged consideration of social and psychological mechanisms of illness causation. Furthermore, later life environmental risk factors may be seen not only as potential etiological factors, but also as both precipitants of illness in the vulnerable and modifiers of the course of illness once begun.

### Drug abuse and dopamine sensitization

The first of the later life risk factors to be considered, drug abuse, straddles the biological and nonbiological. Whether or not drug abuse is a causative factor in the etiology of schizophrenia has long been debated, and the relationship between psychostimulant use and psychotic symptoms has been well documented.[84] Early and larger use of metamphetamine was associated with increased risk of psychosis in a study conducted in Taiwan.[85] The authors also reported that a family history of schizophrenia and premorbid schizoid and schizotypal characteristics appeared to increase vulnerability to the psychosis-inducing effects of stimulant use.

There has recently been particular interest in the idea that cannabis misuse can be a contributing cause for schizophrenia. Certainly, cannabis intoxication is known to precipitate acute psychotic episodes and to worsen symptoms of existing psychotic illness,[86-88] but controversy has surrounded the notion that cannabis misuse could result in a prolonged schizophrenic illness. Andreasson et al[89] prospectively followed up a cohort of Swedish conscripts who had been interviewed about their cannabis use at age 18 to 20 years and found an elevated relative risk (RR) for schizophrenia amongst users compared to nonusers (RR=2.4). In 2002, Zammit et al reanalyzed and extended the data,[90] and found that the association between self-reported cannabis misuse and later risk of schizophrenia persisted after adjustment for other drug use and personality factors. Also in 2002, Arseneault et al presented their findings from Dunedin on a prospective association between adolescent cannabis use and later psychosis.[11] Those using cannabis by the age of 15 years later showed more schizophrenia symptoms than controls and were four times more likely to be diagnosed with schizophreniform disorder, even after psychotic symptoms at age 11 were controlled for (although the latter finding was reduced below significance after adjustment).

In addition to these two studies, there have now been another three large-scale longitudinal investigations in Israel,[91] New Zealand,[92] and the Netherlands[93] all demonstrating a link between cannabis use and later psychosis. Two recent reviews have drawn together the evidence from these longitudinal studies.[94,95] Both conclude that the current evidence has implications for public health messages targeted particularly at vulnerable young people. Arseneault et al[94] calculate that, while on an individual level cannabis use is associated with a twofold increase in RR for schizophrenia, elimination of such use on a population level would reduce the incidence of schizophrenia by approximately 8%. Recent evidence from a Dutch first-onset study also indicates that cannabis use can precipitate an earlier onset of illness and, in fact, they found such use to be a stronger determinant of early onset than gender.[96] Male cannabis users were a mean of 6.9 years younger at illness onset than male nonusers. Thus, there now appears to be increasing evidence that cannabis can trigger the onset of schizophrenia, at least in those who are already predisposed to develop the disorder. Whether cannabis misuse can trigger such illness onset in those not previously vulnerable is still contentious.

Dopamine dysregulation has long been thought central to generation of psychotic symptoms. Evidence for the hypothesis originally derived from the observation that antipsychotics block dopamine receptors while agonists elicit positive symptomatology. More recently, the development of psychosis has been postulated to depend on

dopamine sensitization.[97,98] Sensitization is the process by which repeated intermittent stimulation (eg, by dopamine agonists or indirectly via interaction of other neurotransmitters) produces a progressive and eventually lasting response rather than tolerance.[99] Such sensitization may explain why repeated exposure to drugs of abuse can precipitate psychosis in those predisposed.[97,98] Thus, with repeated cocaine use, psychotic symptoms have been shown to be elicited by progressively smaller doses of the stimulant in studies of cocaine-dependent individuals.[100]
A similar sensitization process could also underlie the precipitation of psychosis in response to repeated exposure to social adversity, as animal studies have shown that stress can lead to dopamine release. Kapur has devised a model where dopamine sensitization links biological, pharmacological, and phenomenological concepts of schizophrenia.[97] He has come to regard psychosis as a state of aberrant salience fuelled by dopamine dysregulation. Sensitization of mesolimbic dopamine pathways, in particular, appears to result in neutral events and stimuli gaining delusional significance for the individual by a process in which excessive release of dopamine results in the abnormal attribution of salience to inconsequential stimuli.[101]

**Migration and risk associated with ethnicity**

The association between migration and schizophrenia has been known for 70 years, and recently Selten and Cantor-Graae have carried out a meta-analysis showing that risk of schizophrenia is significantly increased among immigrants compared to native inhabitants, depending on contextual factors that vary between ethnic groups.[102] In particular, there has been great concern about the high rates of psychosis amongst African-Caribbean immigrants to the UK and their first- and second-generation offspring.[103-106] Overcoming a number of methodological problems highlighted in earlier incidence studies, Harrison et al found that UK subjects born in the Caribbean or who had at least one parent born in the Caribbean, had greatly elevated risks (incidence ratios above 7) for all psychotic disorders including schizophrenia.[107] The phenomenon of excess psychosis is not limited only to African-Caribbean populations in the UK; other migrant groups have also been found to have elevated rates of psychosis. Children born in Greenland to Danish mothers have been found to have RR=3.71 for schizophrenia for example.[108] In the Swedish city of Malmö, immigrants particularly from East-Africa were found to be at increased risk for first-onset schizophrenia-like psychosis compared with native-born controls.[109] The impact of ethnicity and migration on rates of psychosis has further fuelled the debate about the role of social and psychological factors in the etiology of schizophrenia. Sharpley et al have reviewed the current understanding of the role of ethnicity in increasing risk of psychosis.[110] They and others[111] conclude that biological models cannot wholly explain the excess of psychosis observed among African-Caribbean groups in the UK and that factors such as social adversity and psychological theories related to abnormal attributional style may need to be considered. The interaction between ethnicity and the degree of density of the minority in the local neighborhood, for example, has been examined in South London.[112] The risk of schizophrenia appears to be particularly increased among ethnic groups when they comprise a smaller proportion of the local population. In order to further investigate the role of social factors, Mallett et al conducted a first-onset matched case-control study in London between 1991 and 1993.[113] Three socioenvironmental variables separated African-Caribbean cases from both their peers and normal controls: unemployment, living alone, and a long period of separation from their parents in childhood. Eaton and Harrison reviewed 17 population-based studies from the UK and the Netherlands and found that the studies consistently reported higher incidence rates for immigrant groups whose position in society could be described as disadvantaged, with the relative incidence varying from 1.7 to 13.2.[114]

**Urbanicity**

An increased prevalence of psychosis in urban compared to rural settings is one of the most consistent findings in schizophrenia research.[115] Prospective incidence studies are more suited to examining urbanicity as a risk factor for schizophrenia since prevalence studies are limited by migration to urban areas after illness onset. A number of such prospective studies have demonstrated an association between urbanicity at birth or during childhood and later development of psychosis.[108,116] In a recent follow-up study of the entire Swedish population, those living in the most densely populated areas had 68% to 77% more risk of developing psychosis (12%-20% for depression) than the control group living in the least densely populated areas.[117] On the basis of a similar population-based regis-

ter study in Denmark, the proportion of schizophrenia risk attributable to urbanicity was estimated to be as high as 35%.[108] Using the same Danish registers, Pedersen et al recently reported a dose–response relationship between duration of urban exposure during upbringing, rather than at birth, and risk of schizophrenia—evidence that enhances notions of causality.[118] They also found that the RR of schizophrenia increased with changing residence to a relatively more urban area during childhood and adolescence. Mortensen has reviewed the role of urbanicity and suggested a number of intermediate risk factors to explain the association, including toxic exposures, infection, social class, and overcrowding.[119]

There have been concerns about the conceptual validity of urbanicity, the mechanism of causation, and the problem of residual confounding. Van Os has reviewed such concerns and argues that the exposure acts between birth and illness onset, is associated with "at-risk mental states" as well as psychotic disorder, and is likely to reflect social environmental factors such as isolation and poor cohesion.[120] This appears to sit well with the current understanding of ethnic differences in rates of psychosis described above. The finding of Pedersen et al, regarding increased risk following moving residence to a more urban area during childhood or adolescence, may again support notions of the importance of social isolation.[118]

### Social adversity and life events

Many have considered the role of social isolation and social disadvantage in increasing risk of psychosis. The mechanisms explaining associations between social factors and psychosis are likely to be complex, in a similar way to those mediating the roles of ethnicity and urbanicity. Factors such as access to health care, social support, self esteem, unemployment, and poor physical health will play a role.[110] The interaction between perceptions of disadvantage and more direct effects of adversity are also difficult to disentangle. Low social class, a complex concept in itself, has been consistently found to be associated with schizophrenia, but the roles of social causation versus social drift have often been difficult to separate. Studies examining social class at birth, employed as a proxy for assessing social causation, have not been consistent in their findings.[121,122] Byrne et al have recently looked at the role of personal and parental social class in relation to first admission for schizophrenia using data from the Danish national registers.[123] Risk of schizophrenia was associated with unemployment, low educational attainment, being single, lower wealth status, low income, and being childless. Risk was also found to be associated with parental unemployment and parental lower income, but higher parental education. The authors concluded that personal rather than parental socioeconomic disadvantage had the greatest impact on onset of schizophrenia.

Van Os et al found that single people were more likely to develop psychosis if they lived in areas with fewer single people compared to those where being single was apparently more common.[124] As noted earlier, ethnic "minority status" has been found to increase risk of psychosis,[112] and the importance of social adversity has also been raised during discussions regarding the impact of both ethnicity and urbanicity on rates of psychosis. Understanding the nature of social adversity more precisely is clearly an area that warrants further investigation.

Finally, the occurrence of life events has been found to be associated with the onset and later with relapses in psychotic illnesses.[125-127] Initial and early psychotic episodes are more likely than later episodes to be preceded by life events.[128] Affective symptoms, particularly depression, and completed suicide may be precipitated by life events in those with a psychotic illness.[129,130] The effect of personality- or illness-related factors in predisposing to the life events themselves is difficult to remove in these analyses.

## Conclusions

In recent years, we have made substantial progress in recognizing the significance of environmental risk factors in the causation of schizophrenia. We can now confidently discount Bleuler's assertion that schizophrenia occurs independently of external factors. The environment is important throughout the life course. The discovery of prenatal and perinatal risk factors was an important spur to the evolution of the neurodevelopmental hypothesis, but more recently the role of environmental factors nearer to the onset of frank psychosis has attracted much interest, and the role of factors operating in the intermediate childhood period has also begun to be examined. Increasing emphasis has been placed on interaction between genetic and environmental factors. Finally, the elucidation of environmental factors provides us with an opportunity to consider schizophrenia as a potentially preventable disorder.

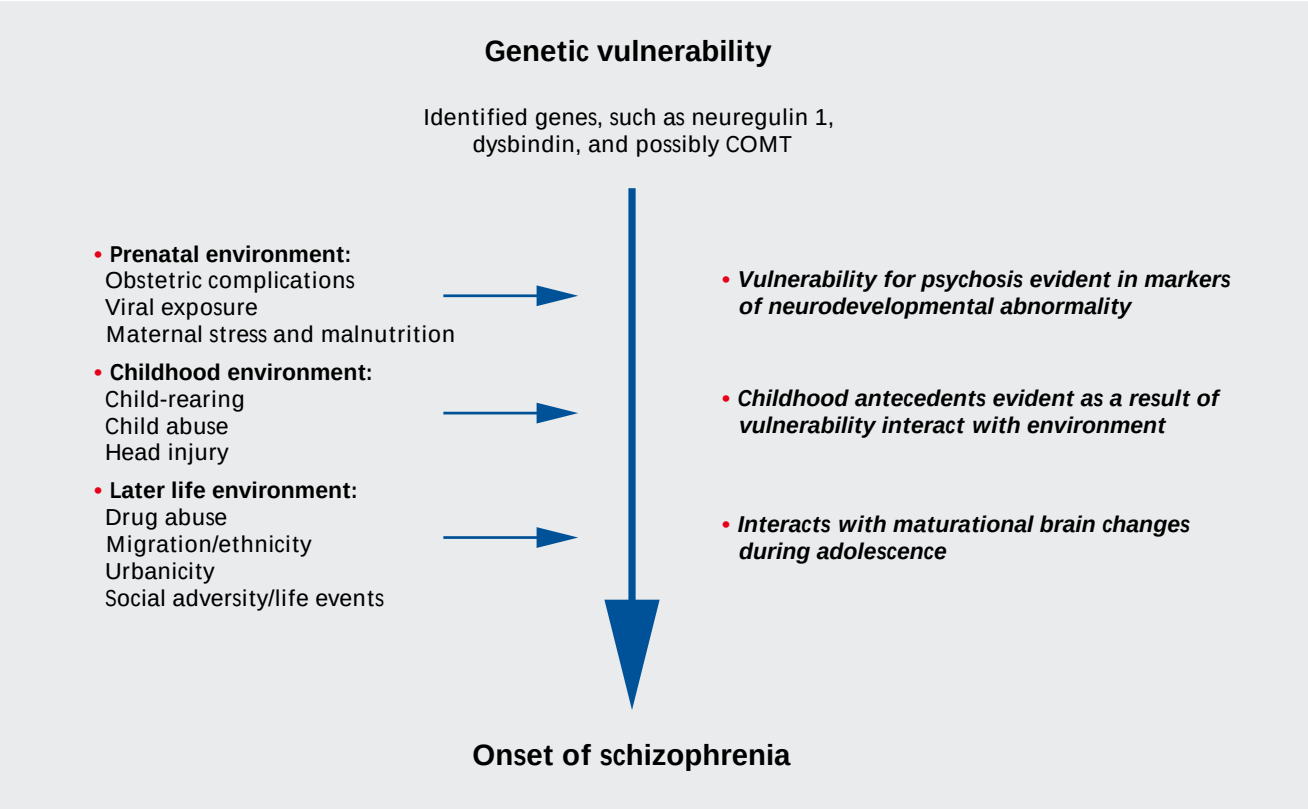


**Figure 1.** Interactions between genetic vulnerability, environmental insults, and the increasingly vulnerable individual. COMT, catecholamine *O*-methyltransferase.

Although environmental risk factors are now seen to operate throughout the life course, they are unlikely to do so in an unrelated manner *(Figure 1)*. The emerging picture is of cumulative environmental (and genetic) risks impacting on the increasingly vulnerable individual in a highly complex manner. Individual risks factors are likely to be correlated with each other and may share causal pathways. Caution and rigor must continue to be exercised with regard to assessment of the validity of findings regarding proposed environmental risk factors, as some may prove spurious. In early life, for example, risk associated with prenatal exposure to infection and obstetric complications is more clearly delineated than that for maternal stress. In later life, the nature of exposures and interrelationships among ethnicity, urbanicity, and social adversity are not yet well understood, while the impact of drug misuse has recently become more certain. The challenge is now further improve the precision with which environmental risks are measured, and to understand the mechanisms of their action and interrelationships. ❑

## REFERENCES


**1.** Bleuler E. Section IX: The causes of the disease. In: Zinkin J, trans-ed. *Dementia Praecox or the Group of Schizophrenias*. New York, NY: International Universities Press Inc; 1950.

**2.** Kraepelin E. Frequency and causes. In: Barclay RM, trans-ed. *Dementia Praecox and Paraphrenia. Edinburgh*, UK: E&S Livingstone; 1919.

**3.** Cardno AG, Marshall EJ, Coid B, et al. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. *Arch Gen Psychiatry*. 1999;56:162-168.

**4.** Tsuang MT, Stone WS, Faraone SV. Genes, environment and schizophrenia. *Br J Psychiatry Suppl*. 2001;40:s18-24.

**5.** van Os J, Sham P. Gene-environment correlation and interaction in schizophrenia. In: Murray RM, Jones PB, Susser E, van Os J, Cannon M, eds. *The Epidemiology of Schizophrenia*. Cambridge, UK: Cambridge University Press; 2003:235-253.

## *Factores de riesgo ambientales para la psicosis*

*Si bien los factores genéticos son claramente importantes en la etiología de la esquizofrenia, el ambiente en el cual se expresan los genes de un individuo también es crucial para el desarrollo de la enfermedad. En esta revisión de los factores de riesgo ambientales para la esquizofrenia se consideran aquéllos que ocurren durante los períodos prenatal y perinatal, durante la niñez y más adelante en la vida, antes de la aparición de la enfermedad. Algunos de estos factores de riesgo han sido bien documentados, como por ejemplo, las situaciones de peligro precoces que provocan retardo del crecimiento fetal o hipoxia y aquéllas más cercanas a la aparición de la enfermedad como el abuso de drogas y la migración. Otros factores de riesgo son mucho menos específicos. La importancia de la interacción entre el riesgo genético y ambiental no está en duda, y la evidencia para esto surge de una variedad de fuentes. Aunque la etiología de la esquizofrenia no esté aclarada, el cuadro clínico se torna más complejo, lo que resulta obviamente más relevante para la difícil situación de cada paciente.*

## *Facteurs de risque environnementaux et psychose*

*Bien que les facteurs génétiques aient un rôle indéniablement important dans l'étiologie de la schizophrénie, l'environnement dans lequel les gènes d'un individu s'expriment est tout aussi crucial pour le développement de la maladie. Cet article passe en revue les facteurs de risque environnementaux de la schizophrénie, tels ceux qui interviennent pendant les périodes prénatale et périnatale, l'enfance et plus tard dans la vie avant le début de la maladie. Quelques-uns de ces facteurs de risque ont été bien documentés, par exemple, les situations agressives précoces provoquant un retard de croissance fœtale ou une hypoxie, et celles survenant à une période plus proche du début de la maladie, comme l'usage de la drogue et l'émigration. D'autres facteurs de risque sont impliqués de façon beaucoup plus incertaine ; néanmoins, le rôle de l'interaction entre le risque environnemental et le risque génétique est indubitablement important, comme en témoigne toute une série d'arguments. Ainsi, plus l'étiologie de la schizophrénie s'éclaircit, plus le tableau de la maladie se complexifie, ce qui ne fait d'ailleurs que correspondre plus réellement à la détresse vécue par chaque patient.*



**6.** Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *BMJ (Clin Res Ed).* 1987;295:681-682.

**7.** Cannon M, Tarrant CJ, Huttunen MO, Jones P. Childhood development and later schizophrenia: evidence from genetic high-risk and birth cohort studies. In: Murray RM, Jones P, Susser E, van Os J, Cannon M, eds. *The Epidemiology of Schizophrenia*. Cambridge, UK: Cambridge University Press; 2003:100-123.

**8.** Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET. Meta-analysis of regional brain volumes in schizophrenia. *Am J Psychiatry*. 2000;157:16-25.

**9.** McGrath J, El-Saadi O, Grim V, et al. Minor physical anomalies and quantitative measures of the head and face in patients with psychosis. *Arch Gen Psychiatry*. 2002;59:458-464.

**10.** Rosanoff A, Handy L, Plesset I, Brush S. The etiology of so-called schizophrenic psychoses: with special reference to their occurrence in twins. *Am J Psychiatry*. 1934;91:247-286.

**11.** Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ*. 2002;325:1212-1213.

**12.** Rosso IM, Cannon TD, Huttunen T, Huttunen MO, Lonnqvist J, Gasperoni TL. Obstetric risk factors for early-onset schizophrenia in a Finnish birth cohort. *Am J Psychiatry*. 2000;157:801-807.

**13.** Verdoux H, Geddes JR, Takei N, et al. Obstetric complications and age at onset in schizophrenia: an international collaborative meta-analysis of individual patient data. *Am J Psychiatry*. 1997;154:1220-1227.

**14.** McNeil TF, Cantor-Graae E, Weinberger DR. Relationship of obstetric complications and differences in size of brain structures in monozygotic twin pairs discordant for schizophrenia. *Am J Psychiatry*. 2000;157:203-212.

**15.** Cannon TD, van Erp TG, Rosso IM, et al. Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. *Arch Gen Psychiatry*. 2002;59:35-41.

**16.** Stefanis N, Frangou S, Yakeley J, et al. Hippocampal volume reduction in schizophrenia: effects of genetic risk and pregnancy and birth complications. *Biol Psychiatry*. 1999;46:697-702.

**17.** Cantor-Graae E, Ismail B, McNeil TF. Are neurological abnormalities in schizophrenic patients and their siblings the result of perinatal trauma? *Acta Psychiatr Scand*. 2000;101:142-147.

**18.** O'Callaghan E, Larkin C, Kinsella A, Waddington JL. Obstetric complications, the putative familial-sporadic distinction, and tardive dyskinesia in schizophrenia. *Br J Psychiatry*. 1990;157:578-584.

**19.** Cannon TD, Rosso IM, Hollister JM, Bearden CE, Sanchez LE, Hadley T. A prospective cohort study of genetic and perinatal influences in the etiology of schizophrenia. *Schizophr Bull*. 2000;26:351-366.

**20.** Harrison PJ, Owen MJ. Genes for schizophrenia? Recent findings and their pathophysiological implications. *Lancet*. 2003;361:417-419.

**21.** Fearon P, Cotter P, Murray RM. Is the association between obstetric complications and schizophrenia mediated by glutaminergic excitotoxic damage in the foetal/neonatal brain? In: Reveley M, Deacon B, ed. *Psychopharmacology of Schizophrenia.* London, UK: Chapman and Hall; 2000:21-40.

**22.** Fearon P, O'Connell P, Frangou S, et al. Brain volumes in adult survivors of very low birth weight: a sibling-controlled study. *Pediatrics*. 2004;114:367-371.

**23.** Nosarti C, Al-Asady MH, Frangou S, Stewart AL, Rifkin L, Murray RM. Adolescents who were born very preterm have decreased brain volumes. *Brain*. 2002;125(Pt 7):1616-1623.

**24.** Bradbury TN, Miller GA. Season of birth in schizophrenia: a review of evidence, methodology, and etiology. *Psychol Bull*. 1985;98:569-594.

**25.** McGrath JJ, Welham JL. Season of birth and schizophrenia: a systematic review and meta-analysis of data from the Southern Hemisphere. *Schizophr Res*. 1999;35:237-242.
**26.** Davies G, Welham J, Chant D, Torrey EF, McGrath J. A systematic review and meta-analysis of Northern Hemisphere season of birth studies in schizophrenia. *Schizophr Bull*. 2003;29:587-593.
**27.** Torrey EF, Miller J, Rawlings R, Yolken RH. Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. *Schizophr Res*. 1997;28:1-38.
**28.** Bagalkote H, Pang D, Jones PB. Maternal influenza and schizophrenia. *Int J Ment Health*. 2001;29:3-21.
**29.** Brown AS. Prenatal infection and adult schizophrenia: a review and synthesis. *Int J Ment Health*. 2001;29:22-37.
**30.** Dean K, Bramon E, Murray RM. The causes of schizophrenia: neurodevelopmental and other risk factors. *J Psychiatr Pract*. 2003;9:442-454.
**31.** Mednick SA, Machon RA, Huttunen MO, Bonett D. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry*. 1988;45:189-192.
**32.** Takei N, Mortensen PB, Klaening U, et al. Relationship between in utero exposure to influenza epidemics and risk of schizophrenia in Denmark. *Biol Psychiatry*. 1996;40:817-824.
**33.** Westergaard T, Mortensen PB, Pedersen CB, Wohlfahrt J, Melbye M. Exposure to prenatal and childhood infections and the risk of schizophrenia: suggestions from a study of sibship characteristics and influenza prevalence. *Arch Gen Psychiatry*. 1999;56:993-998.
**34.** Torrey EF, Bowler AE, Rawlings R. Schizophrenia and the 1957 influenza epidemic. *Schizophr Res*. 1992;6:100.
**35.** Limosin F, Rouillon F, Payan C, Cohen JM, Strub N. Prenatal exposure to influenza as a risk factor for adult schizophrenia. *Acta Psychiatr Scand*. 2003;107:331-335.
**36.** Cannon M KR, Susser E, Jones P. Prenatal and perinatal risk factors for schizophrenia. In: Murray R, Jones PB, Susser E, Van Os J, Cannon M, eds. *The Epidemiology of Schizophrenia*. Cambridge, UK: Cambridge University Press; 2003:74-99.
**37.** Crow TJ, Done DJ. Prenatal exposure to influenza does not cause schizophrenia. *Br J Psychiatry*. 1992;161:390-393.
**38.** Cannon M, Cotter D, Coffey VP, et al. Prenatal exposure to the 1957 influenza epidemic and adult schizophrenia: a follow-up study. *Br J Psychiatry*. 1996;168:368-371.
**39.** Shi L, Fatemi SH, Sidwell RW, Patterson PH. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *J Neurosci*. 2003;23:297-302.
**40.** Brown AS, Cohen P, Harkavy-Friedman J, et al. A. E. Bennett Research Award. Prenatal rubella, premorbid abnormalities, and adult schizophrenia. *Biol Psychiatry*. 2001;49:473-486.
**41.** Suvisaari J, Haukka J, Tanskanen A, Hovi T, Lonnqvist J. Association between prenatal exposure to poliovirus infection and adult schizophrenia. *Am J Psychiatry*. 1999;156:1100-1102.
**42.** Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH. Maternal infections and subsequent psychosis among offspring. *Arch Gen Psychiatry*. 2001;58:1032-1037.
**43.** Brown AS, Begg MD, Gravenstein S, et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. *Arch Gen Psychiatry*. 2004;61:774-780.
**44.** Koponen H, Rantakallio P, Veijola J, Jones P, Jokelainen J, Isohanni M. Childhood central nervous system infections and risk for schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2004;254:9-13.
**45.** Gattaz WF, Abrahao AL, Foccacia R. Childhood meningitis, brain maturation and the risk of psychosis. *Eur Arch Psychiatry Clin Neurosci*. 2004;254:23-26.
**46.** Torrey EF, Yolken RH. *Toxoplasma gondii* and schizophrenia. *Emerg Infect Dis.* 2003;9:1375-1380.
**47.** Kinney D. Prenatal stress and risk for schizophrenia. *Int J Ment Health*. 2001;29:62-72.
**48.** Susser E, Hoek HW, Brown A. Neurodevelopmental disorders after prenatal famine: the story of the Dutch Famine Study. *Am J Epidemiol*. 1998;147:213-216.
**49.** Sacker A, Done DJ, Crow TJ, Golding J. Antecedents of schizophrenia and affective illness. Obstetric complications. *Br J Psychiatry*. 1995;166:734-741.
**50.** Hollister JM, Laing P, Mednick SA. Rhesus incompatibility as a risk factor for schizophrenia in male adults. *Arch Gen Psychiatry*. 1996;53:19-24.
**51.** van Os J, Selten JP. Prenatal exposure to maternal stress and subsequent schizophrenia. The May 1940 invasion of The Netherlands. *Br J Psychiatry*. 1998;172:324-326.
**52.** Selten JP, van der Graaf Y, van Duursen R, Gispen-de Wied CC, Kahn RS. Psychotic illness after prenatal exposure to the 1953 Dutch Flood Disaster. *Schizophr Res*. 1999;35:243-245.
**53.** Huttunen MO, Niskanen P. Prenatal loss of father and psychiatric disorders. *Arch Gen Psychiatry*. 1978;35:429-431.
**54.** Selten JP, Cantor-Graae E, Nahon D, Levav I, Aleman A, Kahn RS. No relationship between risk of schizophrenia and prenatal exposure to stress during the Six-Day War or Yom Kippur War in Israel. *Schizophr Res*. 2003;63:131-135.
**55.** Maki P, Veijola J, Rantakallio P, Jokelainen J, Jones PB, Isohanni M. Schizophrenia in the offspring of antenatally depressed mothers: a 31-year follow-up of the Northern Finland 1966 Birth Cohort. *Schizophr Res*. 2004;66:79-81.
**56.** Barker DJ. *Mothers, Babies and Health in Later Life*. Edinburgh, UK: Churchill Livingstone; 1998.
**57.** Brown AS, Susser ES, Butler PD, Richardson Andrews R, Kaufmann CA, Gorman JM. Neurobiological plausibility of prenatal nutritional deprivation as a risk factor for schizophrenia. *J Nerv Ment Dis*. 1996;184:71-85.
**58.** Jones PB, Rantakallio P, Hartikainen AL, Isohanni M, Sipila P. Schizophrenia as a long-term outcome of pregnancy, delivery, and perinatal complications: a 28-year follow-up of the 1966 north Finland general population birth cohort. *Am J Psychiatry*. 1998;155:355-364.
**59.** Schaefer CA, Brown AS, Wyatt RJ, et al. Maternal prepregnant body mass and risk of schizophrenia in adult offspring. *Schizophr Bull*. 2000;26:275-286.
**60.** Hoek HW, Brown AS, Susser E. The Dutch famine and schizophrenia spectrum disorders. *Soc Psychiatry Psychiatr Epidemiol*. 1998;33:373-379.
**61.** Wahlbeck K, Forsen T, Osmond C, Barker DJ, Eriksson JG. Association of schizophrenia with low maternal body mass index, small size at birth, and thinness during childhood. *Arch Gen Psychiatry*. 2001;58:48-52.
**62.** Susser ES, Lin SP. Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944-1945. *Arch Gen Psychiatry*. 1992;49:983-988.
**63.** Susser E, Neugebauer R, Hoek HW, et al. Schizophrenia after prenatal famine. Further evidence. *Arch Gen Psychiatry*. 1996;53:25-31.
**64.** Hulshoff Pol HE, Hoek HW, Susser E, et al. Prenatal exposure to famine and brain morphology in schizophrenia. *Am J Psychiatry*. 2000;157:1170-1172.
**65.** McGrath J. Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? *Schizophr Res*. 1999;40:173-177.
**66.** McGrath J, Saari K, Hakko H, et al. Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. *Schizophr Res*. 2004;67:237-245.
**67.** McGrath J, Eyles D, Mowry B, Yolken R, Buka S. Low maternal vitamin D as a risk factor for schizophrenia: a pilot study using banked sera. *Schizophr Res*. 2003;63:73-78.
**68.** Ozer S, Ulusahin A, Ulusoy S, et al. Is vitamin D hypothesis for schizophrenia valid? Independent segregation of psychosis in a family with vitamin-D–dependent rickets type IIA. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28:255-266.
**69.** Muntjewerff JW, van der Put N, Eskes T, et al. Homocysteine metabolism and B-vitamins in schizophrenic patients: low plasma folate as a possible independent risk factor for schizophrenia. *Psychiatry Res*. 2003;121:1-9.
**70.** Mirsky AF, Silberman EK, Latz A, Nagler S. Adult outcomes of high-risk children: differential effects of town and kibbutz rearing. *Schizophr Bull*. 1985;11:150-154.
**71.** Cannon M, Caspi A, Moffitt TE, et al. Evidence for early-childhood, pandevelopmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. *Arch Gen Psychiatry*. 2002;59:449-456.
**72.** Agid O, Shapira B, Zislin J, et al. Environment and vulnerability to major psychiatric illness: a case control study of early parental loss in major depression, bipolar disorder and schizophrenia. *Mol Psychiatry*. 1999;4:163-172.
**73.** Jones P, Rodgers B, Murray R, Marmot M. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet*. 1994;344:1398-1402.

**74.** Tienari P, Wynne LC, Moring J, et al. The Finnish adoptive family study of schizophrenia. Implications for family research. *Br J Psychiatry Suppl*. 1994:20-26.
**75.** Read J, Perry BD, Moskowitz A, Connolly J. The contribution of early traumatic events to schizophrenia in some patients: a traumagenic neurodevelopmental model. *Psychiatry*. 2001;64:319-345.
**76.** Garety PA, Kuipers E, Fowler D, Freeman D, Bebbington PE. A cognitive model of the positive symptoms of psychosis. *Psychol Med*. 2001;31:189-195.
**77.** Mullen PE, Martin JL, Anderson JC, Romans SE, Herbison GP. Childhood sexual abuse and mental health in adult life. *Br J Psychiatry*. 1993;163:721-732.
**78.** Read J, Argyle N. Hallucinations, delusions, and thought disorder among adult psychiatric inpatients with a history of child abuse. *Psychiatr Serv*. 1999;50:1467-1472.
**79.** Janssen I, Krabbendam L, Bak M, et al. Childhood abuse as a risk factor for psychotic experiences. *Acta Psychiatr Scand*. 2004;109:38-45.
**80.** Sachdev P. Schizophrenia-like psychosis following traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2001;13:533-534.
**81.** Nielsen AS, Mortensen PB, O'Callaghan E, Mors O, Ewald H. Is head injury a risk factor for schizophrenia? *Schizophr Res*. 2002;55:93-98.
**82.** Wilcox JA, Nasrallah HA. Childhood head trauma and psychosis. *Psychiatry Res*. 1987;21:303-306.
**83.** AbdelMalik P, Husted J, Chow EW, Bassett AS. Childhood head injury and expression of schizophrenia in multiply affected families. *Arch Gen Psychiatry*. 2003;60:231-236.
**84.** Murray RM, Grech A, Philips P, Johnson S. The relationship between substance abuse and schizophrenia. In: Murray R, Jones PB, Susser E, van Os J, Cannon M, eds. *The Epidemiology of Schizophrenia*. Cambridge, UK: Cambridge University Press; 2003:317-342.
**85.** Chen CK, Lin SK, Sham PC, et al. Pre-morbid characteristics and co-morbidity of metamphetamine users with and without psychosis. *Psychol Med*. 2003;33:1407-1414.
**86.** Mathers DC, Ghodse AH. Cannabis and psychotic illness. *Br J Psychiatry*. 1992;161:648-653.
**87.** D'Souza DC, Abi-Saad W, Madonick S, Wray Y, et al. Cannabinoids and psychosis: evidence from studies with iv THC in schizophrenia patients and controls. *Schizophr Res*. 2000;41(special issue):33.
**88.** Hall W, Degenhardt L. Is there a specific "cannabis psychosis"? In: Castle DJ, Murray RM, eds. *Marijuana and Madness*. Cambridge, UK: Cambridge University Press; 2004.
**89.** Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet*. 1987;2:1483-1486.
**90.** Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self-reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ*. 2002;325:1199.
**91.** Weiser M, Knobler HY, Noy S, Kaplan Z. Clinical characteristics of adolescents later hospitalized for schizophrenia. *Am J Med Genet*. 2002;114:949-955.
**92.** Fergusson DM, Horwood LJ, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. *Psychol Med*. 2003;33:15-21.
**93.** van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. *Am J Epidemiol*. 2002;156:319-327.
**94.** Arseneault L, Cannon M, Witton J, Murray RM. Causal association between cannabis and psychosis: examination of the evidence. *Br J Psychiatry*. 2004;184:110-117.
**95.** Smit F, Bolier L, Cuijpers P. Cannabis use and the risk of later schizophrenia: a review. *Addiction*. 2004;99:425-430.
**96.** Veen ND, Selten JP, van der Tweel I, Feller WG, Hoek HW, Kahn RS. Cannabis use and age at onset of schizophrenia. *Am J Psychiatry*. 2004;161:501-506.
**97.** Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry*. 2003;160:13-23.
**98.** Laruelle M, Abi-Dargham A, van Dyck CH, et al. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci U S A*. 1996;93:9235-9240.
**99.** Wolf ME, White FJ, Nassar R, et al. Differential development of autoreceptor subsensitivity and enhanced dopamine release during amphetamine sensitisation. *J Pharmacol Exp Ther*. 1993;264:249-255.
**100.** Bartlett E, Hallin A, Chapman B, Angrist B. Selective sensitization to the psychosis-inducing effects of cocaine: a possible marker for addiction relapse vulnerability? *Neuropsychopharmacology*. 1997;16:77-82.
**101.** Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Brain Res Rev*. 1998;28:309-369.
**102.** Selten JP, Cantor-Graae E. Schizophrenia and migration. In: Gattaz WF, Hafner H, eds. *Search for the Causes of Schizophrenia*. Berlin, Germany: Steinkopff Verlag; 2004:3-25.
**103.** Kiev A. Psychiatric morbidity of West Indian immigrants in an urban group practice. *Br J Psychiatry*. 1965;111:51-56.
**104.** Harrison G, Owens D, Holton A, Neilson D, Boot D. A prospective study of severe mental disorder in Afro-Caribbean patients. *Psychol Med*. 1988;18:643-657.
**105.** Cochrane R, Bal SS. Mental hospital admission rates of immigrants to England: a comparison of 1971 and 1981. *Soc Psychiatry Psychiatr Epidemiol*. 1989;24:2-11.
**106.** Castle D, Wessely S, Der G, Murray RM. The incidence of operationally defined schizophrenia in Camberwell, 1965-84. *Br J Psychiatry*. 1991;159:790-794.
**107.** Harrison G, Glazebrook C, Brewin J, et al. Increased incidence of psychotic disorders in migrants from the Caribbean to the United Kingdom. *Psychol Med*. 1997;27:799-806.
**108.** Mortensen PB, Pedersen CB, Westergaard T, et al. Effects of family history and place and season of birth on the risk of schizophrenia. *N Engl J Med*. 1999;340:603-608.
**109.** Zolkowska K, Cantor-Graae E, McNeil TF. Increased rates of psychosis among immigrants to Sweden: is migration a risk factor for psychosis? *Psychol Med*. 2001;31:669-678.
**110.** Sharpley M, Hutchinson G, McKenzie K, Murray RM. Understanding the excess of psychosis among the African-Caribbean population in England. Review of current hypotheses. *Br J Psychiatry Suppl*. 2001;40:s60-s68.
**111.** Hutchinson G, Takei N, Bhugra D, et al. Increased rate of psychosis among African-Caribbeans in Britain is not due to an excess of pregnancy and birth complications. *Br J Psychiatry*. 1997;171:145-147.
**112.** Boydell J, van Os J, McKenzie K, et al. Incidence of schizophrenia in ethnic minorities in London: ecological study into interactions with environment. *BMJ*. 2001;323:1336-1338.
**113.** Mallett R, Leff J, Bhugra D, Pang D, Zhao JH. Social environment, ethnicity and schizophrenia. A case-control study. *Soc Psychiatry Psychiatr Epidemiol*. 2002;37:329-335.
**114.** Eaton W, Harrison G. Ethnic disadvantage and schizophrenia. *Acta Psychiatr Scand Suppl*. 2000:38-43.
**115.** Freeman H. Schizophrenia and city residence. *Br J Psychiatry Suppl*. 1994:39-50.
**116.** Lewis G, David A, Andreasson S, Allebeck P. Schizophrenia and city life. *Lancet*. 1992;340:137-140.
**117.** Sundquist K, Frank G, Sundquist J. Urbanisation and incidence of psychosis and depression: follow-up study of 4.4 million women and men in Sweden. *Br J Psychiatry*. 2004;184:293-298.
**118.** Pedersen CB, Mortensen PB. Evidence of a dose–response relationship between urbanicity during upbringing and schizophrenia risk. *Arch Gen Psychiatry*. 2001;58:1039-1046.
**119.** Mortensen PB. Urban-rural differences in the risk for schizophrenia. *Int J Ment Health*. 2000;29:101-110.
**120.** Van Os J. Does the urban environment cause psychosis? *Br J Psychiatry*. 2004;184:287-288.
**121.** Harrison G, Gunnell D, Glazebrook C, Page K, Kwiecinski R. Association between schizophrenia and social inequality at birth: case-control study. *Br J Psychiatry*. 2001;179:346-350.
**122.** Mulvany F, O'Callaghan E, Takei N, Byrne M, Fearon P, Larkin C. Effect of social class at birth on risk and presentation of schizophrenia: case-control study. *BMJ*. 2001;323:1398-1401.
**123.** Byrne M, Agerbo E, Eaton WW, Mortensen PB. Parental socio-economic status and risk of first admission with schizophrenia—a Danish national register–based study. *Soc Psychiatry Psychiatr Epidemiol*. 2004;39:87-96.

**124.** Van Os J, Driessen G, Gunther N, Delespaul P. Neighbourhood variation in incidence of schizophrenia. Evidence for person–environment interaction. *Br J Psychiatry*. 2000;176:243-248.
**125.** Leff J, Vaughn C. The interaction of life events and relatives' expressed emotion in schizophrenia and depressive neurosis. *Br J Psychiatry*. 1980;136: 146-153.
**126.** Malla AK, Norman RM. Relationship of major life events and daily stressors to symptomatology in schizophrenia. *J Nerv Ment Dis*. 1992;180:664-667.
**127.** Norman RM, Malla AK. Stressful life events and schizophrenia. I: a review of the research. *Br J Psychiatry*. 1993;162:161-166.
**128.** Castine MR, Meador-Woodruff JH, Dalack GW. The role of life events in onset and recurrent episodes of schizophrenia and schizoaffective disorder. *J Psychiatr Res*. 1998;32:283-288.
**129.** Ventura J, Nuechterlein KH, Subotnik KL, Hardesty JP, Mintz J. Life events can trigger depressive exacerbation in the early course of schizophrenia. *J Abnorm Psychol*. 2000;109:139-144.
**130.** Heila H, Heikkinen ME, Isometsa ET, Henriksson MM, Marttunen MJ, Lonnqvist JK. Life events and completed suicide in schizophrenia: a comparison of suicide victims with and without schizophrenia. *Schizophr Bull*. 1999;25:519-531.