Schizophrenia: The impact of environmental factors

Nadia Saidi

Bachelorthesis Kinder- en Jeugdpsychologie
Universiteit van Tilburg
Faculteit der Sociale Wetenschappen
Departement Psychologie en Gezondheid
Begeleider: Odin van der Stelt, Ph.D.

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Abstract

Schizophrenia is a serious mental disorder arising from the interaction of a range of factors acting at various stages of life. Although a high proportion of liability to schizophrenia is under genetic control, a number of putative environmental risk factors have been identified. This paper will therefore evaluate the current status of early and late environmental factors which influence the pathways to schizophrenia and contribute to risk. This will be carried out by a review of selected relevant literature.

The earliest candidate environmental risk factors include obstetric complications - such as prenatal infections, foetal hypoxia and prenatal maternal nutrition -, maternal life stressors, birth season and birth location. Later candidate environmental risk factors comprise psychological stress factors, personality traits and substance abuse. Some of these risk factors operate on an individual level and some on a societal level but all need to be considered in the context of schizophrenia as a lifelong disorder. It is indispensable to go further than merely documenting the existence of genetic and environmental - both individual and societal - risk factors, to consider how such factors may interact with each other, within the context of development, to produce an outcome of adult psychosis.

Keywords: schizophrenia; aetiology; gene-environment interaction; obstetric complications; adverse life events; substance abuse
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1. Introduction

1.1 Clinical Features

§1.1.1 Prevalence and Symptoms

Schizophrenia is a serious mental illness that afflicts approximately one of every 100 people in the world at some point in their lifetime (American Psychological Association [APA], 2000). The disorder manifests itself in symptoms and signs that encompass the entire range of mental activity (Andreasen, 2000). In the current Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (APA,1994), schizophrenia is described as an illness that is characterized by psychotic symptoms and continuous signs of interpersonal or occupational dysfunction, that persist for a period of at least six months. The term psychotic refers to a loss of contact with reality; patients may have hallucinations (sensory perceptions that have no identifiable external source) or delusions (beliefs that have no basis in reality). The symptoms of schizophrenia can be classified into the general categories of positive and negative. Positive symptoms involve delusions, disorganized thinking and speech, heightened perceptions and hallucinations, and inappropriate affect. Negative symptoms include poverty of speech, blunted and flat affect, loss of volition, and social withdrawal (Comer, 2005). In addition to these more obvious positive and negative symptoms, a third group of symptoms includes cognitive deficits.

§1.1.2 Natural Course

Schizophrenia usually first appears in early adulthood or late adolescence. The modal age at onset is before 25 years. It is relatively rare for preadolescent children to receive a diagnosis, and similarly, it is rare for individuals beyond the age of 40 to experience the illness (Rolf et al., 1992). Recent systematic reviews by Saha and colleagues (2005) indicate that a larger proportion of males meet the DMS-IV criteria for the disorder. It is more likely that - at least a subset of - women have a later onset of illness, as well as a better prognosis and a greater chance of a full recovery (Picchioni and Murray, 2007).

§1.1.3 Treatment

Before the 1900’s, knowledge of the nature and causes of schizophrenia was limited. For more than half of the twentieth century, most people with schizophrenia were institutionalized in a public mental hospital. The primary goal of these establishments were to restrain the patients and give them food, shelter and clothing. They rarely saw a therapist and were
generally neglected. There was little in the way of programs for rehabilitation. Moreover, periods of hospitalization were of longer duration than they are today. This is, in part, due to the deinstitutionalization movement in the 1960’s and the availability today of better medical treatments (Comer, 2005).

It was the discovery of antipsychotic drugs in the 1950’s that truly revolutionized treatment for this disorder. The drugs reduced the symptoms of schizophrenia at least in part by blocking excessive activity of the neurotransmitter dopamine, particularly at the brain’s dopamine D-2 receptors. However, these drugs merely reduced the positive symptoms, but were not effective for the negative and cognitive symptoms. New antipsychotic drugs have been developed in recent years. The most effective and widely used drugs are Risperidone (Risperdal), Clozapine (Clozaril) and ziprasidone (Zeldox). These atypical drugs appear to be more effective than the conventional drugs, helping as many as 85% of people with schizophrenia, compared with the 65% helped by most of the conventional drugs. It is particularly promising that the new drugs cause fewer undesired side effects (Comer, 2005).

However, these atypical drugs also have little or no effect on positive and cognitive symptoms. Consequently, there is a search for novel medications nowadays, based not only on dopamine, targeting the more enduring symptoms of schizophrenia. Clinicians have also used various forms of psychological treatment in an effort to provide therapy for schizophrenic patients. These programs include insight and social therapy, and in recent years, family therapy has become a standard component of the treatment of schizophrenia (Comer, 2005).

1.2 Aetiology

§1.2.1 Genes and Environment

Currently, the most powerful indicator of risk for developing schizophrenia is having a relative afflicted with the disorder. Evidence from a number of “natural experiments” such as twin studies suggests that it is highly heritable, up to 85% (Khashan et al., 2008). Research by Kendler and colleagues (1993) indicates that the risk for developing schizophrenia is 6.5% in first degree relatives of patients, and it rises to more than 40% in monozygotic twins of affected people (Picchioni and Murray, 2007), and to 48% in those persons who have two parents with the disorder (McDonald and Murray, 1999).

It is important to note that in at least 50% of the cases in which one member of a monozygotic twin pair has schizophrenia, the other does not. Such “discordant” pairs have been the subject of a comprehensive investigation in the United States. The most important
findings of this study come from MRI scans conducted on twins. The schizophrenic twins in the pairs showed significantly more brain abnormalities than the healthy twins, which included reductions in the volume of certain brain regions and increases in the size of the ventricles. These results indicate the importance of environmental factors and/or the interaction between genes and these environmental factors (Howes et al., 2003). Other twin studies have shown a concordance rate of approximately 10% in dizygotic twins, as compared to the 40% concordance in monozygotic twins, which indicates that schizophrenia cannot only be due to genetic factors (Andreasen, 2000). Schizophrenic patients probably inherit genes that cause structural brain abnormalities which may be compounded by environmental factors. Certain individuals exposed to an environmental risk factor will have a higher risk of developing schizophrenia, while individuals with a different genotype will be at low risk (McDonald and Murray, 2000). It seems probable that there are several risk genes, which interact with each other and the environmental factors to cause schizophrenia (Picchioni and Murray, 2007). Recent interest has focused on several putative susceptibility genes that present a plausible patho-physiological mechanism to schizophrenia and are particularly relevant to environmental risk factors. These are neurodevelopmental genes, such as neuregulin 1 (NRG1), and genes associated with dopamine regulation, such as the catechol-O-methyltransferase (COMT) gene (Howes et al., 2003). Other susceptibility genes that are associated with schizophrenia include dysbindin (DTNB1), regulator of G-protein signalling 4 (RGS4), disrupted-in-schizophrenia 1 (DISC1) and the novel gene G72 (Harrison and Weinberger, 2005). COMT is the most plausible of the susceptibility genes, because of its role in monoamine metabolism, and because the main genetic variant being associated with schizophrenia is functional (Harrison and Weinberger, 2005).

§1.2.2 Pathogenic Theories

The history of schizophrenia research is filled with widely accepted etiologic theories. When schizophrenia was delineated at the beginning of the 20th century by Emil Kraepelin and Eugen Bleuler, both of these clinical scientists stressed the importance of the defining the illness by attempting to identify a fundamental ‘morbid process’ (Andreasen, 2000). The person with schizophrenia suffers primarily from a fragmenting in cognitive processes; Kraepelin highlighted this aspect when he named the illness “dementia praecox”. Bleuler highlighted the same concept when he renamed the illness “schizophrenia”. The potential role of neurodegeneration was suggested by the original observations of Kraepelin, who characterized schizophrenia by its progressive and deteriorating course. Schizophrenia clearly
fulfills many of the criteria that define neurodegenerative diseases, but it does not exhibit characteristic histopathologic changes and evidence of cell death (Lieberman, 1999). Thus, the ‘founding fathers’ of schizophrenia believed that they had identified a disease that had many different kinds of symptomatic manifestations at the clinical level, but that was in fact defined by an abnormality in a more basic mental process. Their thinking had been reshaped in the 21st century, and expressed by a ‘working model of schizophrenia’, similar to that suggested by Andreasen (2000), shown below.

The neurodevelopmental theory of schizophrenia assumes that the course of normal neural development is disrupted by etiologic and pathogenic factors, long before the formal onset of the disorder, probably during gestation. This results in pathologic changes of specific neurons, and their circuits, ultimately resulting in malfunction. These neurodevelopment abnormalities do not immediately cause clinical manifestations of schizophrenia; they usually present after a latency period of one to three decades. The neurodevelopmental theory further suggests that following its onset, the disorder runs a heterogeneous clinical course, but there are no further neurobiologic consequences beyond those that occur with normal maturational and aging processes and those that might be introduced by treatment effects (Weinberger, 1987, Lieberman, 1999). Despite the substantial evidence of the neurodevelopmental theories, there are certain aspects of schizophrenia that are not adequately explained. Among these are the long latency period and the degenerative clinical course of the disorder. Thus, although there can be little doubt that the neurodevelopmental factors play a role in the pathways to schizophrenia, other pathogenic processes may also be involved (Lieberman, 1999).

Nowadays, recent views emphasize the importance of both early neurodevelopmental and later progressive factors in the pathway to schizophrenia.

Figure 1 Working model of schizophrenia.

Adapted from Andreasen (2000).


§1.2.3 Pathophysiologic Theories

Among the various neurotransmitters that have been implicated in the neuropathophysiology of schizophrenia the tradition emphasizes dopamine. Dopamine is viewed as a candidate for two main reasons: 1) drugs that act to enhance the release or activity of dopamine can produce psychotic symptoms, and 2) drugs that have been established to have antipsychotic properties reduce the activity of dopamine in the brain. Traditional theories have focused on dopamine receptors during the 1950’s. There was indirect evidence that there may be an abnormality in the number of sensitivity of certain dopamine receptors in the brains of schizophrenia patients. Recently, the role of abnormal dopamine release is demonstrated to play a role in schizophrenia by meaning of PET-scans. However, because the dopamine-related drugs merely reduced the positive symptoms, but were not effective for the negative and cognitive symptoms, clinicians started to search for other possible neurotransmitters. Nowadays, several other neurotransmitters have also been hypothesized to play a role in schizophrenia. Current theories include a malfunction of the receptors for the neurotransmitter glutamate and an abnormality in the balance between dopamine and serotonin (Comer, 2005).

Investigators have also described pathophysiologic processes that involve or could lead to neurodegeneration. These implicate N-methyl-D-aspartate (NMDA) receptor hypo function, antagonism of NMDA receptors by N-acetylaspartylglutamate (NAAG) and consequent oxidative stress, reduction in gamma-aminobutyric acid (GABA) interneuron mediated inhibition of pyramidal neurons in the cingulate cortex, DA-mediated neurochemical sensitization, and neurotoxicity as pathogenic mechanisms (Lieberman, 1999).

During the past decade, schizophrenic patients have constantly been reported to have structural brain abnormalities in various anatomic regions of the brain, compared to control subjects. Using computed tomography (CT) and magnetic resonance imaging (MRI) scanning techniques, researchers have found that these patients have abnormal frontal lobes, volume reductions of gray matter in soft tissue structures, and enlarged ventricles; the brain cavities that contain cerebrospinal fluid (Lieberman, 1999). There are also abnormalities reported in the hippocampus, association neocortex (prefrontal and superior temporal) and thalamus (Harrison and Weinberger, 2005). Based on post-mortem evidence of decreased thickness of prefrontal cortex without a reduction in the number of cell bodies, it has been suggested that a reduction of interneuronal neuropil underlies in vivo MRI findings of cortical gray matter reduction in schizophrenia patients (Cannon et al, 2003).

In addition to brain structure, researchers have examined biological indices of brain function in schizophrenic patients. Studies using procedures such as positron emission
tomography (PET) and measurement of regional cerebral blood flow reveal that individuals who suffer schizophrenia have decreased levels of blood flow to the frontal lobes. This is especially the case when these patients perform cognitive tasks (Comer, 2005).

1.3 The search for environmental risk factors
Together, the genetic and biological factors are beginning to unravel the complexity of schizophrenia (Hultman and Öhman, 1998). At the same time, it is important to keep in mind that many people who have these biological abnormalities never develop schizophrenia. Why not? Probably because biological factors merely set the stage for schizophrenia, while key environmental factors must be present for the disorder to appear. For example: Although a great deal of liability to schizophrenia is under genetic control, a number of postulated environmental risk factors have been identified (McDonald and Murray, 1999). The purpose of this paper is therefore to evaluate the current status of early and late candidate environmental factors which influence the pathways to schizophrenia and contribute to risk. This will be carried out by a review of selected recent relevant literature. This paper will highlight illustrative studies, and is not intended to be exhaustive.

Firstly, studies concerning the exposure to early environmental factors will be discussed, and how they may influence the development of the young child. Secondly, a review of the exposure to late environmental factors during adolescence will be specified. Finally, recommendations for further research will be given in the discussion section of this paper.
2. Methods

Suitable relevant literature for this paper was found using the online electronic databases Online Contents University of Tilburg, Web of Science, PsycInfo and Science Direct. Table 1 gives an overview of the databases and keywords that were used. To receive the most relevant literature a minimum of two keywords was used.

The first number mentioned before the mark indicates the number of found publications; the second number indicates the number of publications used for this paper. Articles were selected for this study if they met the following criteria:

- publications were not older than 1996
- articles are published in prestige (impact factor of 2 and higher) scientific journals

Table 1 Output literature search.

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3. Results

3.1 Early environmental factors

§3.1.1 Obstetric Complications

Obstetrical complications (OCs) are defined as physical deviations from the normal course of events during pregnancy, labor, or the neonatal period. Estimates of OCs in schizophrenics have been as high as 67%, significantly higher than the rate OCs found in normal controls (Comer, 2005). Many studies have shown these early environmental ‘insults’, such as prenatal infections, prenatal maternal nutrition, maternal substance abuse, and hypoxia are more common in people with schizophrenia than in the general population (Cannon et al. in Howes et al. (2003)). Three recent studies in particular have been very convincing. Firstly, Jones et al. studied 11,017 Finnish subjects born in 1996 and linked obstetric and psychiatric case registers. The 76 individuals who developed schizophrenia by age 27, were 7 times more likely to have had perinatal brain damage and 6 times more likely to have been born preterm than the residue of the cohort (Jones et al., 1998). Secondly, Geddes et al. carried out a meta-analysis of 11 studies which had used the Lewis scale to interview mothers retrospectively about their offspring’s gestation. Data included 700 schizophrenic patients and 835 control subjects. The OCs particularly implicated included low birth weight, prematurity, being placed in an incubator and premature rupture of membranes (Geddes et al., 1999). Thirdly, in a study using the Swedish national registers, Hultman et al. compared antenatal and delivery records for each of 167 schizophrenic patients with those of five matched controls; similar comparisons against matched controls were also made for 198 patients with affective psychosis and 292 with reactive psychosis. The schizophrenic patients were more likely to have had OCs than both the controls and the affective psychosis and reactive psychosis groups (Hultman et al., 1999).

A. Prenatal infections

As noted earlier, prenatal exposure to maternal viral infection has also been linked with schizophrenia. Specifically, the rate of schizophrenia is increased for cohorts who were in the second trimester during flu epidemics (Rolf et al, 1992). Wright and colleagues have reported that those preschizophrenic neonates whose mothers recalled having influenza in mid-gestation were of lower birth weight and had more perinatal complications than control subjects (McDonald et al., 2000). The focus on prenatal influenza as a risk factor for
schizophrenia has now broadened to include other respiratory tract infections, poliovirus and herpes simplex virus (Cannon et al., 2005).

The Collaborative Perinatal Project (CPP) was a prospective cohort study directed at the identification of perinatal factors with adverse development effects on infant and child. This study observed more than 55,000 pregnancies in 12 study sites in the United States between 1959 and 1966. Cohort mothers were intensively studied during pregnancy and their infants were evaluated for physical and intellectual development during the first 7 years of their lives. Buka and colleagues report the findings from a follow-up study in adulthood of offspring who had been enrolled in the CPP cohort, to test the hypothesis that maternal infections during pregnancy are associated with the development of schizophrenia in adult life. The researchers found that the offspring of mothers with elevated levels of total IgG and IgM immunoglobulins and antibodies to herpes simplex virus type 2 are at increased risk for the development of schizophrenia and other psychotic illnesses in adulthood (Buka et al., 2001).

Recently, Brown and colleagues have claimed that prenatal exposure to rubella is also a risk factor for later schizophrenia. The rubella-exposed subjects, most of who were exposed in the first trimester, demonstrated a substantially greater risk for nonaffective psychosis than the subjects who were not exposed to rubella (Brown et al., 2000).

**B. Foetal Hypoxia**

Complications of delivery that can result in hypoxia also have been linked with heightened risk for the disorder. Hypoxia is a deficiency in the amount of oxygen available to the foetus and can affect the development of various parts of the brain. The hippocampus is known to be susceptible to hypoxic damage (Cannon et al., 2003). Hippocampal volume reduction has been repeatedly demonstrated in schizophrenia. Stefanis and colleagues compared volumetric measurements of the left and right hippocampus, obtained using stereological methods from brain MRI scans, from two groups of patients with schizophrenia as well as healthy controls. 27 patients in the first group, had no family history of schizophrenia and had experienced severe pregnancy and birth complications (PBCs). The second group comprised of 21 patients without a history of severe PBCs from families multiple affected with schizophrenia. Results show that reduction of the left hippocampal volume was associated with the diagnosis of schizophrenia but was present only in patients with a history of severe PBCs; in this group the smaller the hippocampal volume, the earlier the onset of psychosis. (Stefanis et al., 1999).

Stewart and colleagues followed-up a series of 105 children born before 33 weeks into adolescence and compared them with full-term controls. The preterm adolescents had more
neurological, educational and behavioural problems, and were much more likely to show structural brain abnormalities on MRI, especially ventricular dilatation and thinning of the corpus callosum, findings also reported in schizophrenia (McDonald et al., 2000).

C. Prenatal maternal nutrition

Another possible cause of foetal adversity is prenatal malnutrition. A study conducted by Susser and colleagues noted that those exposed to severe malnutrition during the first trimester during wartime famine in Holland were at increased of schizophrenia in adult life (McDonald et al., 2000). Birth cohorts exposed to moderate food deprivation during the first trimester showed a trend toward increased risk of schizophrenia for women. These findings give plausibility to the proposition that early prenatal nutrition can have a gender-specific effect on the risk of schizophrenia. The authors of this study suggest that a micronutrient deficiency could be a risk-modifying factor for schizophrenia. They draw parallels between their data linking prenatal famine and schizophrenia and the links between folate and neural tube defects. The current hypothesis would suggest that the effect of the famine described by Susser and colleagues is mediated via low prenatal vitamin D (McGrath, 1999).

§3.1.2 Maternal life stressors

A population based study by Khashan and colleagues suggests that severe stress to a mother during the first trimester may alter the risk of schizophrenia in offspring. This finding is consistent with ecological evidence from whole populations exposed to severe stressors and suggests that environment may influence neurodevelopment at the fetoplacental-maternal interface (Khashan et al., 2008). Death of a spouse, unwanted pregnancy and experience of catastrophic events such as war, tornado or nuclear explosion have been found to increase the risk of schizophrenia, but not other mental disorders, in offspring in mid-gestation at the time. For example, the five day invasion and defeat of The Netherlands by the German army in May 1940 constituted a severe well-circumscribed national stressful event. Individuals exposed and non-exposed to this stressor in the first, second and third trimester of pregnancy were followed up for lifetime schizophrenia through the National Psychiatric Case Register. Cumulative incidence of schizophrenia was higher in the exposed cohort, which indicates that maternal stress during pregnancy may contribute to the development of vulnerability of schizophrenia (Khashan et al., 2008).
It has been shown that the greatest sensitivity of the developing foetus to stress is during the second trimester of pregnancy, when brain regions relevant to schizophrenia, such as the hippocampus, are developing (Mednick et al., 1998).

§3.1.3 Birth Season
Several studies have found a significant association between risk for schizophrenia and birth in the winter and early spring. This is also true in the southern hemispheres where the seasons are the reverse of the northern hemisphere (Gallagher et al., 1999). Evidence from a number of different countries examined throughout the twentieth century has established that people who become schizophrenic are especially likely to have been born during the winter.

Gallagher and colleagues examined seasonality of birth patterns among a sample of 801 patients with schizophrenia separated into ‘Type I’ and ‘Type II’ schizophrenia. People with Type I schizophrenia are dominated by positive symptoms, such as delusions, hallucinations, and certain formal thought disorders. Those with Type II schizophrenia display negative symptoms, such as flat affect, poverty of speech, and loss of volition. The positive symptoms of Type I schizophrenia seem to be closely linked to biochemical abnormalities in the brain, while the negative symptoms of Type II schizophrenia have been tied to structural abnormalities in the brain (Comer, 2005). Findings indicate that both patient groups were in utero during the winter, but during different trimesters. Patients with Type I schizophrenia were more likely to have been in the womb during the third trimester. Patients with Type II schizophrenia were more likely to be in utero during the first trimester (Gallagher et al., 1999). Although the increase in risk is small, it is notably consistent across studies. Some associate this risk factor with the high number of winter-related viruses, particularly influenza, which can interfere with normal foetal brain development, although malnutrition, vitamin deficiencies, obstetrical complications or other environmental influences during the influences during the early period of pregnancy may also increase the vulnerability for schizophrenia (Hultman and Öhman, 1998).

Some recent studies have suggested that the late winter/early spring births among schizophrenics may be particularly marked among those patients born in urban settings, where population density increases the probability of disease transmission, rather than rural settings (McDonald et al., 2000).
§3.1.4 Birth Location

The incidence of schizophrenia has been shown to increase in a dose related fashion with increasing levels of urbanicity (Mortensen et al., 1999). Lewis and colleagues found that Swedish conscripts who later manifested schizophrenia were 1.65 times more likely to have been brought up in urban than rural areas.

A study by Marcelis and colleagues reported that birth in an urban area of Holland carries twice the risk of schizophrenia of birth in a rural area (Marcelis et al., 1998). In Denmark, those individuals born in Copenhagen have four times the risk of schizophrenia as those born in rural areas (McDonald et al., 2000).

Urban compared to rural living is associated with greater facilitation of the transmission of infections, greater exposure to pollution and stress. Increased health risk behaviours - which are supposed to be more common in urban area – like smoking, drinking and substance abuse may also make individuals more susceptible to developing psychosis by affecting early brain development and/or cognitive schemata (Cannon et al., 2005). These factors will be discussed in the next chapter.

3.2 Late environmental factors

§3.2.1 Psychological stress factors

In adulthood different environmental stressors are active – including social isolation, migrant status and urban life – and this remains the case even when life events attributable to the incipient psychosis itself are excluded (Picchioni and Murray, 2007). Many studies have reported an excess of stressful life events in the few weeks before the onset or relapse of schizophrenic illness (McDonald et al., 2000). Rather than simply peaking in the few weeks before a relapse and acting merely as a trigger, recent studies report an increased rate of life events over a lengthier period prior to the onset of psychosis. Hirsch and colleagues found that life events made a significant cumulative contribution over time (P < 0.05) to the risks of relapse and that ceasing medication made an independent contribution. The risk of relapse increased in proportion to the number of life events but no interaction between medication status and events could be detected; life events were not more closely associated with relapse on medication than off medication. For those of the sample exposed to the mean rate of life events during the study period, it was estimated that 23% of the relapse risk could be attributed to life events, and for those with twice the mean rate of events, 41%. In contrast, patients who continued on regular medication had 80% less risk of relapse than those who had
been withdrawn from medication either by choice or under double-blind controlled conditions (Hirsch et al., 1996).

The Copenhagen risk study demonstrated two distinct developmental trajectories leading to different forms of adult schizophrenia in an admittedly small sample of schizophrenic offspring to severely schizophrenic mothers. Thus, obstetric complications during pregnancy and delivery coupled with extra genetic vulnerability for psychopathology from the father, in combination with problems of social withdrawal at school and low levels of electrodermal activity in the early teens, were prospectively related to a pattern of adult schizophrenia characterised by negative symptoms (Type II Schizophrenia). The alternative developmental pathway included pre-school family disruption, the acting out of behavioural problems at school, and a very active electrodermal pattern in the teens. This combination of factors predicted adult schizophrenia dominated by positive symptoms (Type I Schizophrenia) (Hultman and Öhman, 1998). Such studies lend weight to the idea that social stress can participate both onset and relapse of schizophrenia. However, because causal direction is complicated to establish from retrospective studies, proving it conclusively is difficult (McDonald and Murray, 2000).

The role of social isolation has attracted extensive recent interest. As noted earlier, several studies have demonstrated that being born and raised in an urban area increases the risk of psychosis compared to a rural birth and upbringing (Howes et al., 2003). A study by Allardyce and colleagues demonstrated the incidence of schizophrenia was found to be nearly 2-fold higher in South-London, a deprived inner city area, than in Dumfries, a quiet rural area in Scotland (Allardyce et al., 2000). Social isolation had previously been proposed to be associated with the increased risk of psychosis observed in migrants. Boydell and colleagues investigated the incidence of schizophrenia among people from non-white ethnic minorities in neighbourhoods where they constituted a smaller proportion of the total population. The incidence ratio ranged from 2.4 in areas where the minorities formed a larger proportion of the local population, to 4.4 in the areas where they formed a smaller proportion. Minority populations are not at increased risk of developing psychotic disorders in situations where they become majority population (Boydell et al., 2001). This suggests that social isolation and the lack of social support for people living in an unfamiliar environment may be factors contributing to schizophrenia.

The way parents raise their children does not seem to have a major impact on future vulnerability, but families do have an important part to play in the course of illness. Patients with supportive and caring parents do much better than those with critical or hostile ones, who
experience more stress from their critical parents. The number of critical comments, expressions of hostility, and emotional over involvement comprise a construct referred to as expressed emotion (EE). Recovering schizophrenia patients are much more likely to have a relapse compared with families low in EE. There is also evidence from studies of the adopted offspring of schizophrenia patients suggesting that familial stress can hasten the onset of schizophrenia (Picchioni and Murray, 2007). The quality of parenting seems to interact with genetic predisposition. Tienari and colleagues have shown that when the adopted-away offspring of mothers with schizophrenia are placed in well-adjusted families, they have a lower risk of developing a schizophrenia spectrum disorder than if they are placed in dysfunctional families; the genotype renders the individual susceptible to the effect of an adverse family environment (McDonald and Murray, 2000).

§3.2.2 Personality traits

Some of the risk factors that have been identified for psychiatric illness may be shared between clinically distinct disorders. The identification of shared areas of liability may increase insight into aetiology and treatment (Van Os et al., 1998). Van Os and colleagues studied the risk for schizophrenia associated with neuroticism and extraversion. The personality factor neuroticism - which may reflect instability, vulnerability to stress, or anxiety-proneness - and extraversion rated at the age of 16 were examined in relation to adult schizophrenia in a national birth cohort of 5362 individuals, by means of the short Maudsley Personality Inventory (MPI) at the age of 16, the Present State Examination (PSE) at the age of 36, and the Psychiatric Symptom Frequency Scale (PSF) at the age of 43. The findings from this study suggest that the personality trait neuroticism measured at age 16 increased the risk of later schizophrenia independent of the level of affective symptoms in adult life. The personality trait extraversion measured at age 16 contributes positively to the risk of adult schizophrenia (Van Os and Jones, 2001).

Another personality trait that contributes to the risk for schizophrenia is the schizotypical personality trait. Such individuals are referred to as schizotypes due to the fact that they possess or carry schizotypy, or a latent personality organization that harbors the genetic liability for schizophrenia. The two core defects present in the schizotype's personality organization are 1) a diminished capacity for pleasure, or pleasure deficiency, speculated to have a neurochemical basis deriving from an inherited pleasure potential coded in the infant's genes and 2) a kinesthetic diathesis, which resulted in an aberrant awareness of the body.
Additional schizotypic features are magical ideation, perceptual aberrations and social anhedonia (Lenzenweger, 2006).

§3.2.3 Substance abuse

Problem use of drugs and alcohol by people with schizophrenia is greater than in the general population, but absolute numbers are small. Tobacco use is the greatest problem (McCreadie, 2002). McCreadie and colleagues found that more patients than controls reported problem use of drugs in the past year (7%) vs. (2%) and problem use of alcohol in the past year (17%) vs. (10%). More patients were current smokers (65%) vs. (40%).

The gender difference in age at onset is one of the most consistent findings in schizophrenia research (Veen et al., 2004). Another variable that has been suggested to influence the timing of onset is illicit substance abuse. Psychoactive drug use has become very common in many countries, and may be a factor in the trend towards a lower age of onset of schizophrenia (Howes et al., 2003). Cannabis is the drug most commonly used by people with psychoses, and they often report taking the drug as a type of self-medication. The reasons given include counteracting the negative effects of their medications, or to feel better (Howes et al., 2003). Most studies report a positive association between cannabis use and psychotic disorders, although there are many factors that may affect this relationship. There are a number of potential explanations for this (Degenhardt and Hall, 2002):

1. cannabis could cause psychosis
2. cannabis could precipitate psychosis in vulnerable individuals
3. common factors such as personality disorder could explain the co-occurrence
4. cannabis could prolong psychosis in people with an established psychotic disorder
5. people with psychosis may be more likely to become regular cannabis users because of factors such as self-medication, or social situation and stress.

Prior cannabis use increases the risk of later schizophrenia by a factor of about two and cannabis use in early adolescence is associated with an even larger effect size. For example, in a population-based study by Veen and colleagues, 133 Dutch patients were interviewed with the Comprehensive Assessment of Symptoms and History, and key informants with the Retrospective Assessment of the Onset of Schizophrenia. Milestones of early course were 1) first social and/or occupational dysfunction, 2) first psychotic episode, and 3) first negative symptoms. The results indicate a strong association between the use of cannabis and earlier age at first psychotic episode in male schizophrenic patients (Veen et al., 2004).
Another example, The Dunedin Birth Cohort study, obtained information regarding drug use at ages 15 and 18 years. The use of cannabis at age 15 was associated with a 4-fold increase in the risk of schizophreniform psychosis by age 26.

Another convincing study comes from Andreasson and colleagues who followed up 45,570 conscripts into the Swedish army; those who abused cannabis at 18 years were more likely to be admitted to hospital with schizophrenia over the next decade and a half (McDonald and Murray, 2000). These findings indicate that adolescent cannabis users are at increased risk for experiencing schizophreniform psychosis as adults, over and above childhood psychotic symptoms antedating their cannabis use (Howes et al., 2003).
4. Discussion

This paper indicates that often biological factors merely set the stage for schizophrenia, while key environmental factors must be present for the disorder to appear. The aetiology of schizophrenia involves many factors, which may act from very early development onwards. It appears that familial/genetic factors carry by far the greatest risk, and that the effect size of individual environmental factors is modest. This can be seen in Table 2. Assuming a model in which a number of genes and environmental factors of small effect act additively, the heritability of schizophrenia can be calculated to be between 66% and 85%, thus a high proportion of liability to the disorder is under genetic influence. This study has shown the current status of putative environmental risk factors: early environmental risk factors that contribute to risk include obstetric complications - such as prenatal infections, foetal hypoxia and prenatal maternal nutrition -, maternal life stressors, birth season and birth location. Later environmental risk factors comprise psychological stress factors, personality traits and substance abuse. Some of these risk factors operate on an individual level and some on a societal level but all need to be considered in the context of schizophrenia as a lifelong disorder. However, as noted in this study, it seems that there is often an interaction between genetic susceptibility and environmental effects. Certain individuals exposed to an environmental risk factor will have a higher risk of developing schizophrenia, while individuals with a different genotype will be at low risk (McDonald and Murray, 2000).

The causal role of social factors in schizophrenia is a continuous issue and there are problems with evaluating its contribution. Since many of the likely individual level risk factors, such as experience of chronic stress, are ubiquitous and are therefore extremely difficult to measure. In addition, the use of cannabis is associated with a much earlier onset of the disorder. The explanation for this association still remains unclear. Since early onset is associated with a poorer prognosis of the disorder, the relationship between cannabis use and the risk of developing an early-onset type of schizophrenia is an important focus for future research (Veen et al., 2004). Additional studies examining this possible causal relationship are needed. From an environmental perspective, findings of this paper show the importance of the life-course perspective on schizophrenia as endorsed here. The last few years have seen considerable progress in identifying environmental risk factors for schizophrenia and the beginning of an understanding as to how such factors may interact with genetic predisposition (McDonald and Murray, 2000). It is nonetheless indispensable to go further than merely documenting the existence of genetic and environmental - both individual and societal - risk
factors, to consider how such factors may interact with each other, within the context of development, to produce an outcome of adult psychosis. Findings of this paper also induce a new impetus for specific environmental preventions. These are more practically feasible than interventions at the level of genes and can also help identify who would most benefit from specific tailored environmental intervention. A limitation of this paper is that is it illustrative and not exhaustive. If future research can more clearly identify the environmental causes of specific forms of schizophrenia, clinicians may then be able to make more informed choices as to which therapies are likely to be especially appropriate for particular patients (Gallagher et al., 1999).

Table 2 Risk factors for schizophrenia and their effect sizes.

<table>
<thead>
<tr>
<th>Category</th>
<th>Specific</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>MZ twin</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>DZ twin or sibling</td>
<td>5</td>
</tr>
<tr>
<td>Early environmental</td>
<td>Obstetric complications</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Maternal infection</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>City birth</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Late winter/spring birth</td>
<td>1.1</td>
</tr>
<tr>
<td>Late environmental</td>
<td>Immigrant status</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Chronic cannabis abuse</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Adverse life events</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* Relative risk; b Odds ratio.

Adapted from Cannon and Clarke (2005).
References


\textit{Psychological Medicine, 31}, 1129-1134.
