# What Risk Factors Tell Us About the Causes of Schizophrenia and Related Psychoses

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Genetic, epidemiologic, and molecular studies concur that liability to schizophrenia is transmitted through the inheritance of a number of genes of relatively small effect, some of which are shared with other psychoses. Each of these susceptibility genes causes minor deviations that are relatively innocent in themselves, for example, increased lateral ventricular volume, schizotypal personality, or subtle cognitive difficulties. However, when an individual is unlucky enough to inherit several of these traits, their cumulative effect, often compounded by environmental hazards, propels that person over a threshold for the expression of frank psychosis. Early environmental risk factors for schizophrenia include urban and winter birth, fetal malnutrition and hypoxia, and possibly prenatal viral infections; these early hazards have only a modest risk-increasing effect, and operate in the context of genetic risk. Preschizophrenic children are more likely to have minor psychomotor and cognitive problems; low IQ has a linear relationship with risk for schizophrenia. However, schizophrenia is not simply a neurodevelopmental disorder, because risk factors have been identified that have their effects proximal to the onset of psychosis: drug abuse, immigrant status, and social adversity and isolation. Both genetic and environmental risk factors appear to operate across diagnostic categories and therefore support a dimensional model of psychosis.

## Introduction

If one were to ask a physician the cause of coronary artery disease or diabetes mellitus, the reply would come that there is no single cause; rather, there are a number of genetic and environmental risk factors that interact to cause the illness. So it is with schizophrenia. The incontrovertible conclusion of recent research is that we will not find a single cause, the equivalent of the HIV virus or the Huntington's gene. Instead, schizophrenia, like many other chronic disorders, is a multifactorial disorder subject to a number of risk factors that act together to propel the individual over a threshold for the expression of the condition. When one realizes this, it becomes apparent the etiology of schizophrenia is not a total enigma; rather, we know a lot about the factors that contribute to risk.

Having a relative with psychosis is the most powerful risk factor for schizophrenia, an effect that is genetically mediated, but the 1990s saw a number of large well-designed studies investigating environmental risk factors. Most of these were carried out in Europe where socialized medical systems and national registers offer more opportunity for epidemiologic investigations. Perhaps as a result, research in Europe has diverged from that in North America in two particular ways. First, there has been a growing realization in Europe that schizophrenia is more than a simple neurodevelopmental disorder, and this has led to a renewed interest in social factors [1–3]. Second, the findings of epidemiologic studies are increasingly seen in Europe as incompatible with the traditional Kraepelinian view of psychosis, which postulates that there is a categoric distinction between schizophrenia and affective psychosis; the latter model, however, remains dominant in North America.

## Genetic Risk

The main focus of this review is environmental risk factors, but these operate in the context of genetic risk [4]. Recently, two large twin studies have advanced our understanding of the nature of the latter. Cannon *et al.* [5] examined a Finnish population-based sample of twins with clinically diagnosed schizophrenia, and calculated that about 80% of the variance in liability to schizophrenia was due to additive genetic effects. A report from the Maudsley Twin Register in London produced very similar results, using operational definitions of schizophrenia [6]. As part of the same Maudsley study, Cardno *et al.* [7] asked whether the liability to schizophrenia is specific. The findings indicated that schizophrenia and mania are subject to both shared but also diagnosis-specific genetic

effects. Cardno *et al.* [7] also noted that concordance rates in monozygotic twins were much higher if the proband presented before age 21 years or had poor premorbid function. This implies that some of the susceptibility genes may be involved in neurodevelopment.

Unfortunately, the susceptibility genes for schizophrenia have proved elusive. Owen [8], who provides an excellent review of molecular genetic studies, calculates that if any genes existed that increased the risk of the illness more than three-fold, they would have been found. Thus, it seems that Gottesman and Shields [9] were correct when they suggested 3 decades ago that the genetic predisposition to schizophrenia comprises a number of genes of relatively small effect. Indeed, it may be appropriate to think, not in terms of genes specifically for schizophrenia, but rather in terms of genes determining continuous variation in dimensions of, for example, positive, negative, manic, and depressive symptoms.

## Place and Time of Birth

Several studies [10,11] indicate that being born or brought up in a city is a risk factor for schizophrenia. In one of the most impressive, Mortensen *et al.* [12••] investigated the effect of family history, place, and season of birth on risk of schizophrenia in a large Danish sample; the relative risk associated with urban birth was 2.40, and that with late winter birth was 1.11. This study also established that there is a dose-response relationship for urban birth: the larger the town of birth, the greater the risk. This suggests a causal effect. Mortensen *et al.* [12••] pointed out that because so many people are born and live in cities, a relatively small increase in risk will cause a large increase in numbers of people with the disease. Indeed, they calculated that the population attributable risk (PAF) for urban birth was 34.6%, compared with 9% or 7% respectively for having a mother or father who had schizophrenia. Thus, the effect of urban birth was much larger that the effect of having a relative affected.

As urban birth is strongly correlated with urban residence at the time of onset, Mortensen *et al.* [12••] could not be sure whether the urban risk factor was operating at the time of gestation and birth or around the time of onset. This question was investigated by Marcelis *et al.* [13] in the Netherlands among a cohort of all people born between 1972 and 1978, using a national database that included place of birth and residence. Using population and internal migration data, they characterized the birth cohort as exposed born/exposed resident (EBER), exposed born/nonexposed resident (EBNR), and so on. The relative risk for narrowly defined schizophrenia was 2.05 for EBNR and 1.96 for EBER, implying that there is no additional risk for urban residence at the time of onset, above that of urban birth.

These results point towards an etiologic factor acting in densely populated areas during gestation, birth, or childhood rather than around the time of onset. This could be an infectious agent operating during gestation. As is well known, there is a small but significantly increased risk for schizophrenia and other psychoses among individuals born in late winter and early spring [14]. It was once fashionable to attribute this to an "age-incidence" effect, *ie,* more of the people born early in the year will have developed schizophrenia simply because they are a number of months older. However, this notion cannot be sustained because the excess in the Southern hemisphere occurs in their spring which is in the second half of the calendar year. McGrath *et al.* [15] have carried out an ingenious test of the seasonal effect by examining the dates of birth of schizophrenic patients in Queensland, and contrasted those born in Australia with those who were born in Europe. The latter group showed an excess of births early in the year (*ie,* the European spring), whereas the former group showed the excess later (in the Australian spring).

A large number of studies have addressed the question of whether the spring excess could be secondary to exposure to influenza in utero during the winter. They roughly divide into half suggesting such an effect and half failing to find this [16–20]. Most recently, Westergaard *et al.* [21] investigated the putative link between schizophrenia risk and influenza prevalence during prenatal life in the Danish cohort of 1.75 million people described above. The time period (1950–1988) included the 1957 epidemic. No association for either sex was found irrespective of whether influenza exposure was treated as a categorical or continuous variable.

Because upper respiratory infections are passed on more readily in major conurbations, researchers have inquired whether the season of birth effect is greater in urban than rural settings, several reporting positive results [22,23]. Verdoux *et al.* [24] found a greater season of birth effect in densely populated areas in France (20% excess for > 136 inhabitants per $km^2$). However, the Danish study discussed above did not find any interaction between urban birth and season of birth [12••] or urban birth and exposure to influenza [21].

Other studies have raised the question of whether prenatal exposure to rubella [25] or to malnutrition [26,27] increase risk of schizophrenia, but neither of these findings has yet been replicated.

## Pregnancy and Birth Complications

Many studies have reported an excess of obstetric complications (OCs) in individuals who later develop schizophrenia, but most of these were too small to assess which schizophrenics were most likely to have been exposed and which complications are particularly implicated. To remedy this, Verdoux *et al.* [28] carried out a meta-analysis in which they combined the data from 11 different research groups who used the Lewis-Murray scale. A history of OCs was found in excess in those schizophrenics with onset

under 22 years. This finding has been replicated several times, most recently by Rosso *et al.* [29], who showed that hypoxia-associated OCs significantly increased the odds of early- but not late-onset schizophrenia.

Using the same data set as studied by Verdoux *et al.* [28], Geddes *et al.* [30] reported that the OCs most frequently implicated in schizophrenia were premature rupture of membranes, gestational age less than 37 weeks, and use of resuscitation or incubator. Zornberg *et al.* [31] have also reported on 693 individuals who were born to a community sample of women between 1959 and 1966, and followed-up to age 23 years. Hypoxic ischemia-related fetal and neonatal complications were associated with an increase in the risk of schizophrenia and other nonaffective psychoses: 5.75% compared with 0.39% for those not exposed to such complications.

The most painfully honest report in this field has come from Kendell *et al.* [32], who had previously reported strikingly increased risks of schizophrenia in individuals with a history of OCs [33] in a large case-control study in Scotland. They not only failed to replicate their original findings, but went on to show that these resulted from a problem in the selection of controls. The original, and apparently sensible, way of choosing the controls had in fact selected individuals who had had more healthy births than the general population, thus producing artefactual findings.

Recently, three large epidemiologic studies have come from Scandinavia. Jones *et al.* [34] reported a 28-year follow-up of a 1966 Finnish birth cohort. Children with considerable evidence of perinatal brain damage (especially hypoxia-associated) were seven times more likely to develop schizophrenia, whereas the relative risk associated with prematurity was only slightly less. This study demonstrated that the window of opportunity for risk increasing insults is wider than was previously thought. Those exposed to childhood viral central nervous system infections were five times more likely to develop schizophrenia than those not exposed.

Hultman *et al.* [35••] carried out a population-based nested case-control study of patients with schizophrenia and other psychoses developing up to 21 years. They linked the Swedish birth register from 1973 to 1979 to the nationwide psychiatric inpatient register, and matched five controls to each case. Odds ratios (ORs) were calculated for various events. Schizophrenia was positively associated with multiparity (OR 2), maternal bleeding during pregnancy (OR 3.5), and late winter birth (OR 1.4). Among males an increased risk was found for babies small for gestational age (OR 3.2), fourth or more in birth order (OR 3.6), and whose mothers had bleeding during late pregnancy (OR 4). Weaker associations were found for other psychoses.

Dalman *et al.* [36] carried out a similar study with some of the same probands but compared them with the rest of the birth cohort. They found pre-eclampsia (RR 2.5), vacuum extraction (RR 1.7), and congenital malformations (RR 2.4) were associated with an increased risk of schizophrenia.

The conflicting results between the Scottish and Scandinavian studies need explaining. Only 56% of the records were available in the Scottish study which this excluded births at home or in small units (24% at the start of the study). Differences in the age of probands and in local obstetric practices may also be relevant.

## Childhood Developmental Problems

The 1946 British Birth Cohort Study followed up 4746 children for 43 years. The 30 who developed schizophrenia, as a group, had delayed milestones (walking was delayed 1.2 mo), more speech problems (OR 2.8), lower and declining educational test scores at 8, 11, and 15 years, and a preference for solitary play at 4 and 6 years (OR 2.1) [37]. High-risk studies concur showing that 25% to 50% of children born to mothers with schizophrenia have developmental abnormalities, especially poor motor coordination in early childhood, and attention and information processing deficits later [38,39]. This suggests that developmental problems are at least partly inherited.

There is some evidence that premorbid language, motor, and social impairments are greatest in those schizophrenic patients who present in childhood or adolescence [40,41].

Cannon *et al.* [42•] investigated school performance at 7 to 11 years in Finnish children who later developed schizophrenia, in a case-control study design nested within a population birth cohort of all individuals born in Helsinki between 1951 and 1960. School records were traced for 400 cases and for 408 controls. Cases and controls were compared on three factors: academic, nonacademic, and behavioral after adjusting for sex and social group. Cases performed significantly worse only on the nonacademic factor (mainly sports and handicrafts) but were less likely to progress to a more academic school at age 11, despite being eligible on academic grounds; this suggests personality or motivational problems. The finding that preschizophrenic children performed poorly at sports and handicrafts is consistent with the birth cohort studies and videotapes of children who later developed schizophrenia [43].

The fact that the academic factor did not distinguish between preschizophrenics and controls is in puzzling contrast to other studies. For example, Davidson *et al.* [44] examined assessment scores for nearly 10,000 16- and 17-year-old boys entering the Israeli army. They found that deficits in social functioning, organizational ability, and intellectual functioning predicted later hospitalization with schizophrenia. There was a linear relationship between IQ and risk of schizophrenia.

## Is Low IQ a Cognitive Risk Factor?

David *et al.* [45] also investigated the association between IQ and the later development of psychosis in a population based cohort study of nearly 50,000 18-year-old men who were conscripted into the Swedish army in 1969 and 1970.

By 1983, 195 of the cohort had been admitted to hospital with schizophrenia and 192 with nonschizophrenic psychosis. Tests of verbal ability, visuospatial ability, and general and mechanical knowledge had been carried out at conscription. There was a highly significant association between low IQ scores and the subsequent development of schizophrenia (*eg*, IQ < 74, OR 8.6). Again, the relationship between schizophrenia and IQ was linear with risk gradually increasing as IQ fell at all levels of intellectual ability. The risk for nonschizophrenic psychoses was also higher in those with lower IQ but the effect was less marked and nonlinear. Verbal and mechanical knowledge subtests were independently associated with schizophrenia, but only verbal IQ with other psychoses. The effect size of the low IQ risk factor exceeded that of known environmental risk factors and the distribution was left-shifted, rather than bimodal.

Low IQ may be a confounder (*ie*, brain abnormality leads to schizophrenia and low IQ) but the authors suggest that low IQ is itself a causal factor increasing the risk of schizophrenia. It could act independently or could be one of the means by which other genetic or environmental influences exert their effect, or both. The authors suggest possible mechanisms, *eg*, low IQ could compromise information processing leading eventually to the psychopathology of schizophrenia, or high IQ may be protective.

## Structural Brain Abnormality

Numerous magnetic resonance imaging (MRI) studies have shown structural brain abnormalities in schizophrenia, but many of these are small, case-control studies [46]. There is a consensus that the mean size of the lateral ventricles is larger in people with schizophrenia and to a lesser extent affective psychosis [47]. Jones *et al.* [48] demonstrated a linear trend in the association between lateral ventricle size and risk of onset of schizophrenia. There does not seem to be a sub-group with large ventricles; rather, ventricular enlargement is best conceived as a continuous risk factor.

A number of investigators have asked whether the first-degree relatives of people with schizophrenia show the same abnormalities as their schizophrenic kin. One of the largest of these, the Maudsley family study, has examined patients and well relatives in families with several schizophrenic members; these families were deliberately sampled on the basis that they were assumed to transmit a high genetic loading. Sharma *et al.* [49] carried out MRI scans in patients, well relatives and controls; they further divided the relatives into those who appeared to be transmitting liability to the disorder, *eg*, a woman who, although well herself, had a schizophrenic father and son. These so-called "obligate carriers" showed a similar increase in lateral ventricular volume to the patients themselves; other relatives were midway between patients and controls. Stefanis *et al.* [50] used the Maudsley Family Study samples to show that this is not the whole story. They compared hippocampal volumes in 1) people with familial schizophrenia but no OCs, 2) people with schizophrenia with no family history but severe OCs, and 3) controls. Reduction of the left hippocampal volume was associated with the diagnosis of schizophrenia, but this was accounted for by the patients with a history of severe prenatal and birth complications; patients from the familial group did not differ from controls [50]. This study confirms the claim of McNeil *et al.* [51], that decreased hippocampal volume in schizophrenia is a consequence of hypoxia.

Leonard *et al.* [52] demonstrated that 37 males with schizophrenia could be distinguished from 33 matched controls (age, sex, handedness, parental socioeconomic status) with 77% accuracy by using a cumulative approach to cerebral deviance as shown on MRI; the variables included cerebral and third ventricle volumes, markers of sulcal interruption and disturbed asymmetry in frontal, cingulate, and parietal association cortex. A regression equation using 10 anatomic variables predicted 65% of the variance in full scale IQ in the people with schizophrenia but not the controls. This is an interesting study that needs replicating with larger numbers, an epidemiologic sample, and community controls.

## Gene-environment Interaction

Two aspects of the risk factor model of schizophrenia are initially puzzling. First, how it is schizophrenia appears highly heritable and yet environmental factors appear to play an important role. Second, why is it that the predictive power of each of these environmental factors is low, *ie*, the majority of people exposed to each of the environmental risk factors remain never develop the illness. The unifying explanation seems to be that the environmental factors operate upon genetic risk.

Research into gene-environmental interaction is complicated by our inability to quantify or even identify genetic risk. According to the model proposed by Van Os and Marcelis [53], genetically sensitive individuals are more likely to develop psychosis when exposed to certain environments than others. One example is provided by Cannon *et al.* [54] who found that the odds of schizophrenia increased linearly with the number of hypoxia-associated birth complications, whereas the odds of being an unaffected sibling decreased linearly with the number of hypoxia-associated birth complications. This suggests that part of the genetic vulnerability to schizophrenia is transmitted as susceptibility to the effects of fetal hypoxia; for example, some individuals may be genetically predisposed to excititoxic damage if exposed to hypoxia-ischemia [55].

There are other examples of gene-environmental interaction. In the Finnish Adoptive Family study [56], the risk of developing spectrum disorders was higher in the adopted-away offspring of schizophrenic patients who were exposed to a dysfunctional adoptive family-rearing

environment. The most recent report from this study suggests the adopted-away offspring may have lower risk than children who remain with their schizophrenic parents [57]. Similarly, the Danish-American adoption studies had previously indicated that the adopted-away offspring had a lower risk of later schizophrenia than those who remained with their biologic parents [58]. Mirsky *et al.* [59] noted that children with known genetic risk for schizophrenia were more likely to develop the disorder if they lived on a kibbutz, rather than a family home. Overall, kibbutz children did not have a higher risk, suggesting genetic vulnerability to the social environment in the high-risk children [59].

## Social Risk Factors

It is evident from the above that there has been a revival of interest in the possible effects of the social environment on those with a particular genetic susceptibility. This has stemmed particularly from the evidence that the incidence of psychosis is very high among certain migrant groups and their children [60–62], and the lack of satisfactory biologic explanations for this.

It is well known that migrants have an increased risk of psychosis [63]. For example, in the study of Mortenson *et al.* [12] discussed above, children born in Greenland to Danish mothers had a relative risk of 3.71 for schizophrenia. The most striking findings have come from the United Kingdom, where numerous studies have reported an increased incidence of psychosis among African-Caribbean people [64,65]. Misdiagnosis [66], drug abuse [67], and increased neurodevelopmental insult [68–70] have been largely ruled out as possible explanations. Genetic predisposition cannot be the sole explanation because the increased risk is not shared by the population of origin in the Caribbean [71]. Hutchinson *et al.* [72] found that morbid risks for schizophrenia were similar for parents and siblings of white and first generation African-Caribbean patients. However, morbid risk for siblings of second generation (*ie*, those African-Caribbeans born in the United Kingdom) psychotic probands was approximately seven times higher than that for their white counterparts. This study replicates the work of Sugarman and Crawfurd [73] and suggests the operation of a social risk factor present in the United Kingdom but not the Caribbean.

It is, of course, difficult to identify which are the crucial factors in the social environment. The British 1946 cohort study showed that the quality of the mother-child relationship at age 4 was one of the most powerful risk factors for later schizophrenia; a poor relationship carried a six-fold increase in risk of schizophrenia [37]. However, we do not know the direction of the relationship. Was it poor mothering or was it that the preschizophrenic child could not form a relationship with the mother?

The Swedish conscript study we discussed earlier examined the role of premorbid personality. Young men who felt they were more sensitive than their peers preferred small groups, had fewer than two close friends, and did not have a girlfriend had an increased risk of later developing the disorder [74]. Once again this raises the question of whether these characteristics are an expression of a predisposing schizoid or schizotypal personality or whether they are in themselves independent risk factors. Until proven otherwise, it is wise to consider that both may be true, *ie*, individuals with a schizoid or schizotypal personality may be less able to make social relationships and then the resultant social isolation may propel them further toward frank psychosis.

Van Os *et al.* [75] found evidence for person-environment interaction in Holland. People who were single had a slightly higher risk of developing psychosis if they lived in a neighborhood with fewer single people, compared with a neighborhood with many other single people. The authors suggested that single status might give rise to perceived (or actual) social isolation if most other people are living with a partner. The question of whether social isolation may increase risk of schizophrenia (or whether a close relationship may be protective) is also raised by Jablensky [76], who showed that marriage had a protective effect, and that this was not simply a consequence of better-adjusted men being able to marry.

Three prospective studies have found an association between life events and onset of psychosis [77–79], although the effect size is greater in affective psychosis than schizophrenia. Once again it is difficult to exclude the possibility that some of these events may have been caused by the patient, and thus reflected his or her inherited personality characteristics

## Drug Abuse

Individuals with certain genotypes may select environments that increase risk of the illness. For example, in the Swedish conscript study, Andreassen *et al.* [80] found that individuals, who at age 18 had abused cannabis, had an increased risk of being admitted to hospital with schizophrenia over the next 13 years. Consumption of cannabis on more than 50 occasions by the age of 18 years, was associated with a six-fold increased risk of later developing schizophrenia; the dose response relationship suggested causality.

Evidence that some of the 18-year-olds may have been taking the cannabis as an attempt at self-treatment came from the finding that over half of those who admitted to taking cannabis at age 18 already had a psychiatric diagnosis. However, even when these individuals were excluded, cannabis consumption remained a risk factor for later psychosis. McGuire *et al.* [67] have shown that the relatives of individuals with cannabis-associated psychosis have a particularly high morbid risk of psychosis. Thus, it may be that some individuals abuse cannabis because they are genetically predisposed to have psychiatric difficulties, and it is these individuals among the larger population of cannabis users who are particularly likely to develop psychosis.

## Implications of Risk-factor Research for Our Models of Psychosis

For more than a century, the dominant model of psychosis has been a categorical one based on Kraepelin's distinction between schizophrenia and manic-depressive psychosis. Indeed, this view of psychosis, exemplified by the DSM (*Diagnostic and Statistical Manual of Mental Disorders*) system, has now achieved almost a monopoly of thought in the United States. In contrast, dissatisfaction with the Kraepelinian dichotomy has now become a major driving force for European research [81].

Two major problems with the Kraepelinian model have always been that 1) many patients have features of both schizophrenia and affective psychosis, and 2) there is remarkable heterogeneity even within the category of schizophrenia. There has been a long search for subtypes of schizophrenia. For example, Murray *et al.* [82] sought to distinguish developmental and adult onset forms. Support for this came from latent class analyses but there remained the problem of intermediate forms [83,84].

This view had to be modified because of the evidence reviewed above that both the genetic and environmental risk factors operate across diagnostic categories [85,86]. The revised model suggests that a spectrum of psychosis that is under the influence of two major effects exists. The first "neurodevelopmental impairment" is evidenced by family history of chronic psychosis, OCs, childhood impairment, and cerebral ventricle enlargement, and has maximal effect in chronic cases (mostly males with early onset and poor outcome). The second effect arises when social adversity acts on a genetic predisposition to affective psychosis. This factor exerts maximal effect at the acute onset, good outcome pole of psychosis. At the extreme ends of the continuum, neurodevelopmental and social/affective etiologies predominate respectively, but in many of the intervening cases both etiologic factors are operating.

Much evidence suggests that factors influencing the persistence of psychosis also operate across categories [87], and pharmacologic response is symptom- rather than diagnosis-specific. A number of factor analytic studies of symptoms have produced three psychotic dimensions (positive, negative, and disorganized) and two affective dimensions (mania and depression) [88,89]. In short, across academic centers in Europe, a dimensional approach to psychotic phenomena is becoming accepted as having greater etiologic validity and greater utility for treatment and prognosis than a categorical one [90,91•].

Research is now proceeding in two directions. The first is to elucidate the mechanism by which individual risk factors operate. The second is to build coherent models of the way in which different risk factors interact to influence the onset of the disease and then its outcome.

## Acknowledgments

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