Schizophrenia in Society
An Epidemiological Perspective

Preben Bo Mortensen

Department of Psychiatric Demography, Institute for Basic Psychiatric Research,
Psychiatric Hospital in Aarhus, Risskov, Denmark

Contents

Summary

Schizophrenia is a disorder of major public health concern both in terms of occurrence and cost. It affects approximately 1% of the population. Although the causes and pathogenesis of schizophrenia are not known in any detail, there is strong evidence that both genetic and 'environmental' risk factors are important in the aetiology of this disease. Environmental risk factors include: urban birth, urban upbringing, seasonal birth, influenza, infections during pregnancy, obstetric complications and higher risk in lower social classes. The condition is often chronic even though progress has been made both in psychopharmacological treatment and in psychosocial interventions. The patient's ability to work is often impaired, and schizophrenia is associated with increased mortality both from suicide and natural causes of death.

Schizophrenia is probably one of the most extensively studied disorders within the field of psychiatric epidemiology. The literature on schizophrenia epidemiology, i.e. the occurrence of and risk factors for schizophrenia has already been the subject of several reviews including Jablensky and Eaton,[1] and Eaton.[2] The aim of this paper is to give a general overview of current consensus and controversies in schizophrenia epidemiology, including some key references to papers and reviews that should allow the reader to find relevant literature within their particular field of interest.

1. The Occurrence of Schizophrenia

There are a number of studies on both preva-
lence and incidence of schizophrenia. This litera-
ture has been described extensively in the reviews
mentioned above.[1,2] Generally, prevalence data
are more useful for estimating the burden of illness
in society, including cost of illness. However, inci-
dence rates and, more specifically, the distribution
of incidence rates relating to age, sex and other
factors, is more informative for the formulation of
aetiological hypotheses.

Prevalence rates have been highly variable[3]
with at least 10-fold differences across popula-
tions. However, even when considering these large
regional variations in prevalence, it would not seem
unreasonable to expect an average prevalence be-
tween 3 and 5 per 1000 people in most populations.
The incidence, i.e. the number of new cases of the
disease in a defined base population within a given
time, is only known from very few general popu-
lation studies, e.g. the Lundby Study.[4] Also, due
to the difficulties which are discussed later in this
section, it will often be difficult to generalise the
results from these studies.

Studies are often based on figures from first hosp-
italisations or first contacts to a treatment setting.
In most studies, crude rates per 1000 per year will
vary between 0.15 and 0.30. Finally, other than
prevalence and incidence, a third measurement of
disease occurrence, lifetime risk, is an estimate of
the risk for any individual in a population to expe-
rience even one schizophrenic episode during their
expected lifetime, is assumed to be approximately
1%.[5]

Studies of the occurrence of schizophrenia face
a number of problems. First, the initial onset of
schizophrenia in any given population will be a
relatively uncommon event making it necessary to
study large populations to get precise rate esti-
mates. Secondly, it requires skill and training to
conduct the necessary interviews to establish the
diagnosis of schizophrenia. This, in connection with
the need to study large populations, may make it
prohibitively difficult to conduct general popula-
tion incidence studies. Studies based on treatment
settings will be biased by the selection factors into
those treatment settings. Finally, even relatively
large studies are often too small to make exact ad-
justments for basic risk factors such as age and sex,
making results difficult to compare.

The literature supports the idea that schizophre-
nia is occurring with relatively constant frequency
around the world. However, even in the only study
directly comparing rates in various cultures there
was about a 2-fold difference from the highest to
the lowest lifetime expectancy.[6] These differences
were not statistically significant, but may have
been influenced by sample size and other method-
ological problems. *In summary,* incidence studies
or studies of the risk of developing schizophrenia
are difficult to conduct, and the literature does not
exclude the possibility of considerable variation in
disease risk within different populations.

2. Decreasing Incidence of Schizophrenia?

A large number of studies during the 1980s and
1990s, based mainly on hospitalisation data, have
suggested that the incidence of schizophrenia may
be decreasing.[7,8] This literature has been reviewed
recently by Munk-Jørgensen.[9] This literature sug-
gests that a real decrease may have taken place dur-
ing the 1970s and 1980s primarily in England,
Wales, Scotland and Denmark, as well as in New
Zealand. However, a number of methodological
problems such as decreasing availability of hospi-
tal beds, changing diagnostic habits and other fac-
tors, may have contributed to the decrease in first
hospitalisation rates for schizophrenia. Therefore,
the decrease in these rates or first contacts does not
necessarily reflect a real decrease in the occurrence
of the disorder in the general population.

3. Risk Factors for Schizophrenia

3.1 Genetics

A family history of schizophrenia is by far the
most firmly established risk factor for this disorder.
Gottesman[5] generated average lifetime risks for
developing schizophrenia according to family re-

lation to schizophrenic patients on the basis of about 40 western European studies conducted from 1920 to 1987. The risk of developing schizophrenia in monozygotic twins to schizophrenic patients (probandwise concordance rate) is approximately 48% whereas there was a 17% risk in dizygotic twins. Children of schizophrenic parents have about 13% morbid risk and siblings to schizophrenic patients have 9% risk.[5]

These data, together with the results of adoption studies,[10] make it clear that genetic factors, not only shared experiences or other environmental factors, are important in the causation of schizophrenia. Further evidence came from studies of the offspring of discordant monozygotic twins[11] which showed almost equal risk in the offspring of the schizophrenic and the non-schizophrenic twins.

Interestingly, twinning itself may be a risk factor for schizophrenia. Kläning et al.[12] have reported an increased risk in twins compared with single-born in a population-based study. The impact of this finding on the interpretation of twin studies is not clear at present.

Although much effort has gone into the field of molecular genetics of schizophrenia within the past decade, there are no final breakthroughs in this field. However, there is significant evidence for loci conferring liability to schizophrenia in chromosomes 6p, 8p and 22q, with partial replication, and suggested evidence for loci on the short arm of chromosomes 3, 9 and 20.[13] Molecular genetics continue to be one of the most rapidly developing fields in the area of schizophrenia aetiology.

3.2 Sex

Lifetime risk for schizophrenia is generally assumed to be the same in males and females, although this assumption is subject to the same uncertainties discussed in connection with general studies of the occurrence of schizophrenia. There is general agreement that onset is later in female than in male patients. In males, onset is generally in the early to mid-twenties whereas the majority of studies find that the mean age of onset in females is 4 to 5 years later.[14]

Some studies have indicated that male patients have poorer outcome than female patients, but this may be explained by the earlier age of onset in males as early age of onset in itself is a predictor of poor outcome.[15,16] Also, in the recent study by Kendler and Walsh,[17] no differences in a 15-year outcome were found between male and female patients. The authors suggested that differences in how males and females used services and sought care may explain sex effects in non–epidemiologically-based follow-up cohorts.

3.3 Environmental Risk Factors

As suggested by the concordance rates given above, the fact that only approximately half instead of all monozygotic twins to patients with schizophrenia themselves develop schizophrenia, indicate that nongenetic factors are important in the aetiology of this disease, as monozygotic twins are genetically identical. Most of these possible risk factors are believed to act through mechanisms affecting the development of the brain during embryonic and fetal life. A number of the relevant theories regarding neurodevelopmental risk factors for schizophrenia have been summarised in a recent book by Waddington and Buckley.[18] These environmental risk factors will be reviewed briefly in sections 3.3.1 to 3.3.5.

3.3.1 Urban Birth or Urban Upbringing

It has been consistently demonstrated that the prevalence of schizophrenia is higher in urban than in rural areas.[19] Selective migration has been suggested as the cause of this finding, but urban birth, not only urban residence at the time of onset, has been found to be a risk factor for schizophrenia.[20]

Lewis et al.[21] reported an increased risk associated with urban upbringing, even after adjusting for family history of mental disorders as well as substance abuse. The increased risk associated with urban birth or upbringing is thus a fairly robust finding, but the cause of this is unknown.

3.3.2 Season of Birth

An excess of individuals born during winter and spring months among schizophrenic patients is

among the most frequently replicated findings in the schizophrenia epidemiology.[22-24] Lewis[23] has proposed this finding to be largely a methodological artifact, but this is unlikely. Although frequently replicated, the causes of this finding are still not known. The months of birth most frequently reported to be associated with increased schizophrenia risk are December through March in the majority of studies conducted in the northern hemisphere. The few studies from the southern hemisphere have generally been smaller, and results less consistent.

In a large study, McGrath et al.[25] compared rates of schizophrenia in individuals born in the southern hemisphere to those born in the northern hemisphere who had later immigrated to Australia. They found an excess both in those born in the northern hemisphere in March to April, as well as in those born in the southern hemisphere winter (July to September).

This winter birth excess is possibly not specific to schizophrenia as a similar pattern has been described in bipolar disorder.[26] Possible explanations for this finding, apart from methodological problems, include a different procreational pattern over the year in individuals predisposed to schizophrenia, increased exposure to environmental risk factors, such as maternal influenza and obstetric complications (see section 3.3.4), as well as maternal dietary insufficiency.

The possible role of dietary insufficiency during pregnancy as a risk factor for adult schizophrenia is largely based on one study by Susser and Lin.[27] The association has also been related to seasonal variation in stillbirths.[26,28] Variations in temperature have been suggested,[29] but could not be replicated in a second analysis including data from Scotland, England and Denmark.[30] It has been suggested that the winter birth excess in schizophrenia is confined to urban born patients with the strongest relation in female patients, but this finding needs further replication. Also, it is still a subject of controversy whether the season of birth differs between patients at low and high genetic risk for schizophrenia (for review see Cotter et al.[24]).

In summary, the relationship between season of birth and schizophrenia risk seems to be firmly established but the causes of this pattern are still unknown. Even though the winter/spring excess is modest (5 to 15%) and has no predictive value for any individual, it is still a finding that must be confronted by any aetiological theory for schizophrenia.

3.3.3 Influenza and Schizophrenia

Since the study by Mednick et al.[31] in Helsinki relating adult schizophrenia to the prenatal exposure of an influenza epidemic, a number of studies have replicated the relationship between population rates of influenza especially during the second trimester of pregnancy and later schizophrenia.[30,32-34] Wright and Murray[35] have hypothesised that maternal antibodies induced by influenza infection may cause fetal brain damage by cross-reacting with brain antigens. Thus, a proportion of schizophrenia may represent an autoimmune disease by proxy because antibodies of maternal origin are elicited by the influenza virus in immunogenetically predisposed women.

Most studies demonstrating a relationship between influenza during pregnancy and adult schizophrenia have not been based on data regarding infection in the individual mothers of later schizophrenic patients. These have been ecological studies relating population rates of schizophrenia to population rates in the cohorts in mid-trimester of pregnancy during high exposure periods. In the few positive studies relating individual data and infection during pregnancy,[36,37] recall bias cannot be excluded.

To date, direct studies of children to women exposed to influenza have been negative.[38] However, these studies are generally too small to be taken as evidence against an association between schizophrenia and prenatal influenza infection.

Some studies have found the effect of influenza on schizophrenia risk to be confined to females,[39] but the possible sex differences in schizophrenia risk and influenza remain unresolved.

At present, influenza is probably one of the most plausible environmental risk factors in schizophre-

nia epidemiology. It should be noted that our knowledge is not sufficient to justify any particular warnings or risk estimates for women who are exposed to influenza during mid-trimester pregnancy. Also, other infections have been suggested as possible risk factors for schizophrenia. These include various infections during fetal life or early childhood transmitted through cats or other household pets,[40] or CNS infections, e.g. meningitis during early childhood.[41]

3.3.4 Obstetric Complications

Obstetric complications have been associated with increased schizophrenia in a large number of studies.[42-45] A recent meta-analysis of the existing studies[46] concluded that children exposed to obstetric complications were twice as likely to develop schizophrenia, but also that the observed association could be inflated by both selection and publication bias. Furthermore, it has been suggested that the association could be ascribed to an increased occurrence of obstetric complications among females with a predisposition towards mental disorders, i.e. not a causal effect.[47] This hypothesis, however, has not been substantiated by data, and the nature of this predisposition has not been specified.

The specific nature of complications that particularly increase schizophrenia risk has not been identified with any certainty. One specific factor, rhesus incompatibility, has been suggested,[48] but this would only apply to a minority of cases. *In summary,* the literature suggests that a causal role of obstetric complications in schizophrenia is very likely but more research is needed to clarify the specific nature of this relationship.

3.3.5 Social Class

It has been an early observation that the prevalence of severe mental disorders including schizophrenia was higher in those of lower social class compared with high social class.[49,50] These findings are largely accepted, but the explanation for this is the subject of a continuing debate.

One explanation is a social causation theory which hypothesises that factors associated with lower social class status are implicated causally in the development of serious mental illness.[51] The social selection drift perspective hypothesises that the association between social class and serious mental illness is a result of the illness impairing an individual's social class attainment and/or an individual's drifting down in social class status after the onset of the illness.[51] Many researchers favour the social drift hypothesis[52] whereas others cannot find the evidence sufficient to exclude a causal effect of social class.[51]

There would not seem to be any logical reason why the two explanations should mutually exclude each other. Also, it would seem very plausible that other risk factors for schizophrenia, e.g. maternal infections during pregnancy or obstetric complications, are associated with low social class. In other words, associations between the current social class of individuals and their risk for developing schizophrenia would not necessarily mean that their current social environment is responsible. However, it might suggest that it is closely correlated to living conditions during fetal life or early childhood related to increased exposure to the risk factors.

4. Economic Aspects

Although schizophrenia only constitutes a minority of the total psychiatric morbidity in general populations, patients with schizophrenia have a relatively high utilisation of hospital beds and other services in psychiatry. Munk-Jørgensen and Mortensen[8] estimated that after the initial first 6 months following first admission with schizophrenia, patients will, on average, spend approximately 10% of their remaining lifetime as psychiatric inpatients.

In a recent report for the Danish Medical Research Council,[53] utilisation of hospital beds for different diagnoses was compared. Schizophrenia was the highest ranking single diagnosis with approximately 500 000 hospital days compared with the second highest consuming disorder, cerebrovascular disorder (387 000 bed days), and the third most important, fracture of the femur (277 000 bed

days). Schizophrenia, therefore, constituted about a quarter of all psychiatric hospital bed days.

In the US, Wyatt et al.[54] estimated the annual cost for schizophrenia in 1991 to total $US65 billion based on the estimate of about 3 million Americans between 18 and 65 years old with schizophrenia. The costs were distributed as $US18.6 billion direct costs and $US46.5 billion indirect costs. The majority of the direct costs were costs of inpatient and outpatient care and medication, whereas the majority of the indirect costs were the loss of productivity due to suicide, lost productivity in the family of the patient and lost compensation to the families.

It would seem clear from these figures that schizophrenia is a disease of major public health importance. This is still a fact even if a large minority of patients (approximately 30 to 40%) improve significantly, as shown in a recent meta-analysis of the outcome literature.[55] Also, early pharmacological and psychosocial interventions may further improve course and outcome, as recently suggested.[56]

In summary, apart from what this disorder imposes on the patient and his or her family, it is a disorder associated with costs comparable to disease groups such as cardiovascular disorders or cancer where the public health importance is more widely acknowledged. This is often not realised when allocating funds for treatment and research.

5. Suicide and Other Causes of Death

Some are not aware that mental disorders including schizophrenia can be fatal and are often associated with a very high mortality. This excess mortality is dominated by suicide.[57] Generally, 10 to 15% of patients with schizophrenia are assumed to commit suicide,[58] but even this figure may be too low. Based on a sample of first-time hospital admitted schizophrenic patients, we estimated 'life-time risk for suicide' to be about 20 to 25%.[59] A number of risk factors for suicide in schizophrenia have been identified,[58] including young age, male sex, social isolation and depression.

It has been of some concern that deinstitutionalisation may have been accompanied by an increase in suicide risk among schizophrenic patients. In our study,[60] the risk within the first year after first schizophrenia hospitalisation had increased by 50% during in the same period in which the number of hospital beds had been reduced by 50%. A recent analysis of the same data[61] confirmed that this temporal trend could be explained by changes from longer towards shorter admission with more frequent readmissions, or so-called 'revolving door' patients.

Mortality is also increased for most natural causes of death. One notable exception in several studies has been cancer. Some reports of this can be explained through methodological problems but some large studies have found significant reductions in cancer risk in schizophrenic patients.[62,63] It is possible that this can be partly explained by an anti-neoplastic effect of some neuroleptics,[63,64] but this still needs further empirical validation.

6. Conclusions

It has only been possible within the limits of this paper to give a somewhat brief outline of the epidemiology of schizophrenia. It should hopefully be clear from this review that schizophrenia is a disorder of major public health concern, of both genetic and environmental origin. It is a disorder where much research still remains before we get closer to its aetiology and possible prevention.

Progress is being made with increasing speed. Perhaps the most promising perspective is the advances made within molecular genetics. This is not only because of the direct implications of findings from these studies but in terms of our understanding of the pathophysiology and possible treatment of the disorder. More direct measurement of the genetic risk factors for this disorder is exactly the information the epidemiologist needs in order to design more efficient studies of the environmental risk factors.

Future aetiological studies in schizophrenia must include both genetic and environmental risk factors, as is the case in the study of other mental disorders.[65] This would also help to change the current usefulness of epidemiological evidence

which presently is something primarily of interest for research and planning purposes. This epidemiological evidence could be applied in a situation where knowledge about risk factors may be of more direct value in the counselling and management of the individual patients and in the primary prevention of schizophrenia.

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About the Author: Preben Bo Mortensen is a senior scientist at the Department of Psychiatric Demography where he conducts studies in psychiatric epidemiology, especially within the fields of schizophrenia and affective disorders as well as general studies of the epidemiology of suicide.
Correspondence and reprints: Dr *Preben Bo Mortensen*, Department of Psychiatric Demography, Institute for Basic Psychiatric Research, Psychiatric Hospital in Aarhus, Skovagervej 2, 8240 Risskov, Denmark.