

Why factors rooted in the family may solely explain the urban-rural differences in schizophrenia risk estimates

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Abstract. Many studies have identified urban-rural differences in schizophrenia risk. The underlying cause(s) may hypothetically include toxic exposures, diet, infections, and selective migration. In a recent study, we concluded that some of the cause(s) responsible for the urban-rural differences in schizophrenia risk are rooted in families, but some might also be rooted in individuals. First, we describe temporality as a potential methodological pitfall within this line of research, then we review studies not subject to this pitfall, and finally, we describe why factors rooted in the family may solely explain the urban-rural differences. Although other potential explanations for these differences exist, we focus on this hypothesis as it has not previously been discussed in detail. To determine the cause(s) responsible for the urban-rural differences, we need direct measurements of genetic and/or environmental factors related to urban life.

One of the intriguing questions in the epidemiology of schizophrenia is why people who are born and raised in an urban area are more likely to develop schizophrenia compared to people born and raised in a rural area. Urban life in itself is not likely to increase the risk of schizophrenia. Rather, urbanicity must be a proxy variable for some unknown underlying cause(s) more (or less) prevalent in urban areas. These cause(s) have been hypothesized to include diet, infections, stress, obstetric complications, toxic exposures, social class, and artefacts of selective migration (Freeman 1994; Mortensen, 2000; Pedersen & Mortensen, 2006a).

Also, no compelling evidence exists of whether the urban-rural differences are due to causal or non-causal explanations. Although there is no necessary or sufficient criterion for determining whether an observed association is causal, the cause must precede the effect in time (temporality). Although, this criterion is inarguable for causality, lack of temporality provides no evidence for or against causality (Rothman & Greenland, 1998).

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review studies not subject to this pitfall, and finally, we describe why factors rooted in the family may solely explain the urban-rural differences. Although other potential explanations for these differences exist, we focus on this hypothesis as it has not previously been discussed in detail.

TEMPORALITY

For a study to be potentially informative of whether urban-rural differences are due to causal effects (the cause-and-effect hypothesis), temporality must be satisfied, i.e., the cause (urbanization) must precede the effect (schizophrenia) in time. Therefore, ideally we should measure urbanization prior to the earliest stage of the disease process rather than the onset of signs or symptoms. However, in schizophrenia research we are often faced with problems in accessing the time of onset of the disorder, meaning that if we simply measure urbanization at first registration/diagnosis with schizophrenia we may well fail the criterion of temporality. It seems reasonable to assume that if we measure urbanization at birth or at least prior to the 15th birthday, the cause (urbanization) will precede the disorder or its prodromata.

Although places of residence at consecutive time-points during upbringing are strongly associated, temporality seems very important with a disorder as schizophrenia where people are expected to migrate towards the city as a consequence of the disorder or its prodromata. Surprisingly, such migration has never been established empirically.

In the following, we review findings where the exposure (urbanization) has been measured prior to the pro-

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dromal phase of schizophrenia, which we have defined at the 15th birthday. Such studies are not subject to any bias due to selective migration of the individual due to the disorder or its prodromata. Though some studies do not satisfy these strict criteria, we acknowledge that urban-rural differences have been observed quite consistently throughout the world.

REVIEW OF URBAN-RURAL DIFFERENCES IN THE RISK OF SCHIZOPHRENIA

Lewis *et al.* (1992) identified a dose response association between being brought up in urban areas and having schizophrenia later in life which persisted despite adjustment for other factors associated with city life such as cannabis use, parental divorce, and family history of psychiatric disorder. Lewis followed 49191 conscript males aged 18-19 years in 1969-1970 for development of schizophrenia from 1970 to 1983 (268 people developed schizophrenia). Urbanization was based on responses to questionnaires such as "Where did you live mostly while you were growing up?". Conscripts who reported any psychiatric symptoms at start of follow-up were interviewed by a psychiatrist and were excluded from the study if they were diagnosed with schizophrenia.

Mortensen *et al.* (1999) were the first to identify urban-rural differences in the incidence of schizophrenia in Denmark: Adjusting for a history of schizophrenia in a parent or sibling, people born in the capital (Copenhagen), the capital suburb, a provincial city, a provincial town, or a rural area, had a relative risks of 2.14 (2.13-2.70), 1.62 (1.37-1.90), 1.57 (1.36-1.81), 1.24 (1.10-1.41), and 1.00 (reference category), respectively. In these data there was virtually no interaction (on the multiplicative scale) between place of birth and a family history of schizophrenia. Mortensen *et al.* (1999) effectively followed 1.3 million people born to Danish women in 1955-1978 from their 15th birthday to 1993 (2669 people developed schizophrenia).

Torrey *et al.* (2001) found evidence of geographical clustering of the incidence of schizophrenia according to 217 areas of birth in Denmark. This geographical clustering was solely explained by age, gender and urbanization at birth, thus suggesting that the five-level classification of the degree of urbanization used in Denmark encompassed the geographical clustering of schizophrenia in Denmark. Torrey *et al.* (2001) used almost the same study population as Mortensen *et al.* (1999). In contrast to these Danish findings, Haukka *et al.* (2001) found evidence of geographical clustering of the incidence of

schizophrenia according to 57 areas of birth in Finland, which was not explained entirely by age, gender, birth cohort, and urbanization at birth.

Pedersen & Mortensen (2001b) replicated the study by Mortensen *et al.* (1999) in a larger sample. The increased risk associated with urban birth could not be explained by inadequate adjustment for mental illness in family members, and it was invariant to the diagnostic system used, the inclusion of out-patient information, the classification of urbanization used, and potential bias in the selection of the study population used by Mortensen *et al.* (1999). Pedersen & Mortensen (2001b) effectively followed 1.7 million people born in Denmark in 1955-1983 from their 15th birthday to 1998 (10264 developed schizophrenia).

A Danish study by van Os *et al.* (2004) found that the risk of schizophrenia in people with a family history of schizophrenia, psychosis, or any psychiatric admission was higher (on the additive scale) if they had been born in urban areas compared to rural areas, and that 20%-35% of the individuals exposed to both urbanicity and family history of schizophrenia had developed schizophrenia because of the synergistic action of the two proxy causes. However, one of the classic problems in epidemiological research is how to describe/model the joint action of two exposures (here urbanization and family history). Since these results were based on an additive model (change in risk occurs by adding a quantity) as opposed to a multiplicative model (change in risk occurs by multiplying a quantity), and that (except for special cases) absence of interaction on the multiplicative scale implies interaction on the additive scale (and vice versa), these results were indeed in agreement with the lack of interaction on the multiplicative scale between urbanization at birth and a family history of schizophrenia presented by Mortensen *et al.* (1999). There is neither any consensus nor any easily accessible description of choice of additive versus multiplicative model (but see (Andersen, 2004; Clayton & McKeigue, 2001; Greenland, 1993). In absence of such knowledge, we suggest to choose a model that describes the observed data with as few parameters as possible. Irrespective of the model chosen, interactions should be interpreted with caution, and more specifically statistical interactions do not necessarily translate into biological interactions.

A Finnish study showed that urban birth emerged as a risk factor for schizophrenia among people born 1960-1969 and that urban birth had no effect among people born in 1950-1959 (Haukka *et al.*, 2001), a Dutch study showed that the effect of urban birth was strongest in the youngest birth cohorts (Marcelis *et al.*, 1998), and a Danish study found no evidence of time trends in the

urban-rural differences in the incidence of schizophrenia among people born in 1945-1986, but found that young people (< 20 years) had a slightly greater risk associated with urban birth compared to older people (Pedersen, 2006). In the Danish data, urban birth was also strongest in the youngest birth cohorts, but this finding was entirely explained (confounded) by the stronger effect of urban birth for young people. Haukka *et al.* (2001) followed people born in Finland in 1950-1969 from the 15th birthday to 1991 (14828 people with schizophrenia), Marcellis *et al.* (1998) followed people born in the Netherlands in 1942-1978 from 1970 to 1992 (16716 people with broadly defined schizophrenia), Pedersen (2006) followed people born in Denmark 1955-1986 from their 15th birthday to 2001 (11500 people with schizophrenia). Except for the lack of an urban effect among those born in Finland in 1950-1959 these results seem quite consistent.

Pedersen & Mortensen (2001a) investigated the potential association between the risk of schizophrenia and urbanicity at birth and during upbringing, and found 1) that the period of exposure associated with the urban-rural differences ranged from birth to at least the 15th birthday, 2) no age periods during upbringing were associated with particular vulnerability to residence in urban areas, 3) among individuals moving to a higher degree of urbanization during upbringing, the risk of schizophrenia increased, while among individuals moving to a lower degree of urbanization, the risk decreased, and 4) the effect of urbanicity at birth was explained by the effect of urbanicity during upbringing. These results were based on people born in Denmark in 1956-1983 who were followed from their 15th birthday to 1998, of which 8235 people developed schizophrenia. On the basis of those findings, we concluded that continuous or repeated exposures incurred during upbringing that occurred more frequently in urbanized areas might be responsible for the association between urbanization and schizophrenia risk and that candidate risk factors would include infections, diet, and exposure to pollution.

Later, a study based on a small sample showed an association between air pollution from traffic and schizophrenia risk (Pedersen *et al.*, 2004), but a nationwide study showed that the geographical distance to nearest major road - used as a proxy for traffic related exposures from traffic - had no impact on the risk of schizophrenia, indicating that traffic related exposures may thus be less likely explanations for the urban-rural differences in schizophrenia risk (Pedersen & Mortensen 2006b).

Until now, research in the cause(s) responsible for the urban-rural differences has focussed on cause(s) linked entirely to the individual by investigating the potential

association between place of birth and upbringing and the risk of schizophrenia. In a recent study, we investigated whether the cause(s) responsible for the urban-rural differences in the risk of schizophrenia were rooted in individuals or in families (Pedersen & Mortensen, 2006a). We evaluated whether older sibling's place of birth had an independent effect on schizophrenia risk when controlling for the individual's place of birth and place of residence during upbringing. If the cause(s) responsible for the urban-rural differences in the risk of schizophrenia were rooted in individuals, the nearest older sibling's place of birth should have no independent effect. However, we found that the nearest older sibling's place of birth had an independent effect on the risk of schizophrenia. We concluded that some of the cause(s) responsible for the urban-rural differences were rooted in families, but some might also be rooted in individuals. In the paper, we offered three additional potential explanations of the urban-rural differences in schizophrenia risk: 1: Accumulation of risk exposures during the family's residence in urban areas, 2: some families had a genetic liability related both to the family's migration towards the city and the risk that their children would develop schizophrenia, and 3: some families had a familial trait linked to the environment related both to the family's migration towards the city and the likelihood that they would be exposed to some unknown risk factors for schizophrenia and/or are more vulnerable to such factors.

WHY FACTORS ROOTED IN THE FAMILY MAY SOLELY EXPLAIN THE URBAN-RURAL DIFFERENCES

Hypothesize that the urban-rural differences in the risk of schizophrenia are rooted entirely in the family, then all previous urban-rural findings comply with this hypothesis:

First, due to the correlation between places of residence throughout the lifespan (i.e., people born in a rural area are also more likely to be growing up there etc.), place of birth of a child would be a proxy variable of the family's urban residence, and the papers identifying urban-rural differences at place of birth or at any other time-point would agree with our hypothesis.

Second, place of residence during upbringing would be an even better proxy variable of the family's urban residence than place of birth. This would explain all previous findings including: 1) that the period of exposure associated with the urban-rural differences ranged from birth to at least the 15th birthday, 2) no age periods during upbringing were associated with particular vulnerability

to residence in urban areas, 3) among individuals moving to a higher degree of urbanization during upbringing, the risk of schizophrenia increased, while among individuals moving to a lower degree of urbanization, the risk decreased, and 4) the effect of urbanicity at birth was explained by the effect of urbanicity during upbringing (Pedersen & Mortensen, 2001a). In that study, we concluded that continuous or repeated exposures during upbringing that occur more frequently in urban areas might be responsible for the association between urbanization and schizophrenia risk. Our previous interpretation was based on the belief that choice of residence is random. Two recent Australian and Dutch studies showed that this is not the case as they found a genetic and/or shared familial contribution to the choice of residence (Whitfield *et al.*, 2005; Willemsen *et al.*, 2005).

Third, in a recent study (Pedersen & Mortensen, 2006a) we found that among persons whose nearest older sibling had been born in the capital area, place of birth had no effect, while place of residence during upbringing had a weak non-significant impact on the risk of schizophrenia. Since the individual's place of residence during upbringing is encompassed entirely by the family's urban residence, we cannot distinguish the potential effect of the individual's urban residence during upbringing from the potential effect of the family's urban residence (place of residence during upbringing serve both as a proxy variable of the family's urban residence after the child's birth and of the individual's urban residence during upbringing). Therefore, all results in this recent study may comply with the hypothesis that the urban-rural differences are rooted entirely in the family.

We have thus argued that factors rooted entirely in the family may solely explain the urban-rural differences in the risk of schizophrenia. Though other potential cause(s) responsible for these differences exists, we focussed on this hypothesis as it has not been discussed in the literature.

Currently, we have no evidence of what causes the urban-rural differences in the risk of schizophrenia. We do not even know whether these differences represent causal or non-causal effects. If these are causal we also do not know whether these are due to genetic factors, environmental factors, or a combination of these factors. One obvious study with the potential ability to distinguish genetic from environmental factors, would match schizophrenic people individually with their healthy siblings. However, as siblings live together during upbringing such an approach is unfruitful (Pedersen & Mortensen, 2006a). How do we proceed?

Our view is that we need direct measurements of genetic and environmental factors related to urban life.

Therefore, we initiated a project which links data from the Danish PKU bank (filter blood samples from all births in Denmark since 1981), the Danish Psychiatric Central Register, and the Danish Civil Registration System. We aim to study the effects of and interactions between genetic polymorphisms and measures of environmental risk factors as infectious agents, cytokines, obstetric factors, urbanicity and other suspected risk factors for schizophrenia. The birth cohort in the PKU-bank currently includes 950 people with schizophrenia. The number of cases will increase rapidly over the next few years.

Danish researchers are very fortunate that the Danish Civil Registration System (CRS) includes person-identifiable information on all Danes along with their family relations, that the CRS has recorded and kept historical person-identifiable information on place of residence for all Danes since 1971 (Pedersen *et al.*, in press), that the Danish Psychiatric Central Register includes virtually complete person-identifiable registration of Danes with schizophrenia since 1971 (Munk-Jørgensen & Mortensen, 1997), and that Danish legislation allows Danish researchers access to these valuable data (The Danish Civil Registration Office, 2005). These factors make Denmark an ideal setting in which to explore the cause(s) responsible for the urban-rural differences in the risk of schizophrenia.

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