



# Persons with schizophrenia migrate towards urban areas due to the development of their disorder or its prodromata



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## ABSTRACT

**Background:** Many studies have identified urban–rural differences in the occurrence of schizophrenia. Though unknown, the underlying causes responsible for these differences have been hypothesized to include urban–rural differences in toxic exposures, diet, infections, stress, or an artifact due to selective migration. Freeman hypothesized that persons with schizophrenia migrate towards larger cities due to development of their disorder or its prodromata. Based on this, the reason for the high frequency of schizophrenia in urban areas is not that those affected have lived in environmentally unfavorable areas, but that people with schizophrenia selectively migrate towards urban areas due to disease onset. No population-based studies assessed the extent and potential impact of this artifact of selective migration.

**Methods:** Utilizing a population-based sample of the Danish population, it was investigated if persons with schizophrenia more often migrated towards larger cities due to disease onset. The impact of selective migration on the urban–rural differences was quantified comparing a prospective and a retrospective study.

**Results:** Compared to healthy controls, persons with schizophrenia spectrum disorder migrate to a higher degree of urbanization due to disease onset (OR = 1.18 (1.14–1.23)). However, the bias in urban–rural effect sizes due to this artifact of selective migration was limited.

**Conclusion:** Persons with schizophrenia drift towards urban areas as a consequence of the disorder or its prodromata, but this drift has only limited impact on the urban–rural differences. Therefore, prospective and retrospective studies are both informative on the unknown underlying factor or factors responsible for the urban–rural differences in schizophrenia risk.

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## 1. Introduction

Many studies have identified urban–rural differences in the occurrence of schizophrenia (March et al., 2008). Though unknown, the underlying causes responsible for these differences have been hypothesized to include urban–rural differences in toxic exposures, diet, infections, stress, or an artifact due to selective migration (Freeman, 1994; Mortensen, 2000).

Freeman hypothesized that persons with schizophrenia migrate towards larger cities due to the development of their disorder or its prodromata, or fail to participate in the general movement of mentally healthy persons away from larger cities (Freeman, 1994). If true, this selective migration of persons with schizophrenia will increase the prevalence of persons with schizophrenia in urban areas. From this viewpoint, the reason for the highest prevalence of schizophrenia in urban areas is not that affected individuals have lived in environmentally

unfavorable areas, but that people with schizophrenia selectively migrated towards urban areas due to the development of their disorder or its prodromata. Thus, being a resident in an urban area is not an etiological factor in itself, but rather a consequence of the development of the disorder.

Although the drift hypothesis was first described by Lapouse et al (1956) and later by Freeman (1994), no population-based studies investigated whether persons with schizophrenia migrated towards larger cities more often than healthy controls due to the development of the disorder (Lesage and Tansella, 1989). If persons with schizophrenia more often migrate towards urban areas than healthy controls, previous studies reporting urban–rural differences in the prevalence of schizophrenia present upward biased estimates, whereas studies reporting urban–rural differences in the incidence rate of schizophrenia will have no such bias. Both methods were applied in this study to enable a comparison.

There were two main aims to the present study. First, it was investigated if persons with schizophrenia and schizophrenia spectrum disorders migrated towards larger cities more often than healthy controls during disease onset (i.e., identify any selective migration). The second

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aim was to quantify the potential impact of selective migration on the urban–rural differences in the prevalence of schizophrenia and schizophrenia spectrum disorder.

This is the first study to utilize a nationwide population-based sample to quantify the potential selective migration of persons with schizophrenia towards urban areas due to the development of the disorder or its prodromata.

## 2. Methods

When the Danish Civil Registration System (Pedersen et al., 2006) was established in 1968, all people alive and living in Denmark were registered. From 1968 onwards, it includes information on personal identification number, sex, date and place of birth, continuously updated information on vital status, and historical information on place of residence. Today 5.8 million persons live in Denmark. The personal identification number is used in all national registers, enabling accurate linkage among registers. The study population consisted of all persons who were born in Denmark from 1 January 1955 to 31 December 1997 and whose parents were both born in Denmark.

### 2.1. Assessment of schizophrenia and schizophrenia spectrum disorder

The study population was linked with the Danish Psychiatric Central Research Register (Mors et al., 2011) to obtain information on mental disorders. From 1969, the Danish Psychiatric Central Register contains data on all admissions to Danish psychiatric in-patient facilities, and from 1995 it also contains information on all contacts to out-patient psychiatric departments and visits to psychiatric emergency care units. All Danish residents are entitled to free national health care; there are no private psychiatric hospitals in Denmark, and all visiting patients are registered in the Danish Psychiatric Central Research Register. From 1969 to 1993, the diagnostic system was the Danish modification of the International Classification of Diseases, 8th revision (ICD-8) (World Health Organization, 1971). From 1994, the International Classification of Diseases, 10th revision, Diagnostic Criteria for Research (ICD-10-DCR) (World Health Organization, 1993) was applied. Individuals were classified with schizophrenia and schizophrenia spectrum disorder if they had been admitted to a psychiatric hospital, received outpatient care, or visited a psychiatric emergency care unit with a diagnosis of schizophrenia (ICD10: F20 and equivalent ICD8-codes) or schizophrenia spectrum disorder (ICD10: F20–F29 and equivalent ICD8-codes (Pedersen et al., 2014)). The date of onset was defined as the first day of the first contact (inpatient, outpatient or psychiatric emergency care unit) diagnosed with the relevant diagnosis.

### 2.2. Classification of urbanization

Place of birth and residence in Denmark were classified according to the degree of urbanization (Statistics, 1997) (numbers are persons per square kilometer): capital 5220; capital suburb 845; provincial cities 470; provincial towns 180; rural areas 55, as done previously (Pedersen, 2006). Residential information on municipality from 2007 onwards was transformed into the original 276 municipality units to allow for a consistent classification of the degree of urbanization at place of residence throughout the study period. Denmark is a small homogeneous country with a population of 5.8 million people and a total area of 43,000 km<sup>2</sup>.

### 2.3. Study design and statistical analyses

Within the study population, persons who had their first diagnosis with schizophrenia and/or schizophrenia spectrum disorder between 1973 and 2007 were identified. In order to compare with the general mobility of the Danish population, for each case, 10 controls were identified. The controls had the same sex, were born within 1 day from the

case, they were alive, residing in Denmark and not diseased at the time the matched case became a case.

### 2.4. Assessment of urban–rural drift

For cases and controls separately, the degree of urbanization at their place of residence two years before onset was contrasted with the degree of urbanization at their place of residence five years after onset. Place of residence two years prior to onset was used to account for possible selective migration during the prodromal phase of the disorder (Freeman, 1994; Thorup et al., 2007).

### 2.5. Assessment of impact of urban–rural drift

To quantify the impact of selective migration on the urban–rural differences in the occurrence of schizophrenia, two competing methods were applied: the odds ratio of *being* diseased and the incidence rate ratio of *becoming* diseased. The odds ratio of being diseased was estimated as the odds of being diseased at each degree of urbanization divided by the odds of being diseased in a rural area. This study design is retrospective, i.e. it is based on prevalent sampling. Persons who were alive and resident in Denmark 5 years after the case became a case contributed to the prevalent sample. The odds ratio of being diseased was estimated using ordinary logistic regression adjusting for age and sex.

The incidence rate ratio of becoming diseased (i.e., the risk of becoming diseased) was estimated as the incidence rate of the disorder at each degree of urbanization divided by the incidence rate of the disorder in a rural area. This study design is prospective, which means it is based on incident sampling. Persons who were diagnosed with the disorder contributed to the incident sample, irrespective of later emigration or death. The incidence rate ratio was estimated using conditional logistic regression (SAS Institute Inc., 2008) with each matched case–control set forming a separate stratum. Owing to the matching scheme, all estimates were adjusted for sex and age.

## 3. Results

During the period 1973–2007, 26,352 persons born in Denmark 1955–1997 were diagnosed with schizophrenia spectrum disorder for the first time in their life. Table 1 shows characteristics of the cases and controls at baseline (when the case was first diagnosed) and at follow-up (five years after the case became a case). Since controls were matched individually to cases according to sex and age, cases and controls had an identical distribution of age and sex (Table 1). Table 1 also shows characteristics at follow-up. Among schizophrenia spectrum disorder cases, 4.36% died within 5 years of onset and 0.63% emigrated from Denmark. During the same time period, 0.41% of the healthy controls died and 1.64% emigrated.

Among the 24,583 persons with schizophrenia spectrum disorder who were alive and resident in Denmark 5 years after onset, 69.5% remained on the same degree of urbanization, 16.5% moved to a higher degree of urbanization, and 14.0% moved to a lower degree of urbanization (Table 2). Among the 257,319 healthy controls, 72.2% remained on the same degree of urbanization, 16.4% moved to a higher degree of urbanization, and 11.4% moved to a lower degree of urbanization. Comparing cases to healthy controls, this corresponds to an odds ratio for an upward drift of persons with schizophrenia spectrum disorder of 1.18 (1.14–1.23) and downward drift of persons with schizophrenia spectrum disorder of 1.05 (1.01–1.19) (Table 2).

To evaluate the specificity of this finding, the potential urban–rural drift of persons with narrowly defined schizophrenia is also shown in Table 2. Compared to healthy controls, persons with narrowly defined schizophrenia had an odds ratio for upward drift of 1.12 (1.07–1.18) and an odds ratio for downward drift of 0.98 (0.93–1.03).

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