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Population impact of familial and environmental risk factors for schizophrenia: A nationwide study

Holger J. Sørensen [a,d,*], Philip R. Nielsen [b,d], Carsten B. Pedersen [b,c,d], Michael E. Benros [a,b,d], Merete Nordentoft [a,d], Preben B. Mortensen [b,c,d]

[a] Psychiatric Centre Copenhagen, Capital Region of Denmark, University Hospital of Copenhagen, Bispebjerg Bakke 23, 2400 NV, Denmark
[b] National Centre for Register-Based Research, Aarhus University, Business and Social Sciences, Aarhus, Denmark
[c] Centre for Integrated Register-based Research, CIRRAU, Aarhus University, Aarhus, Denmark
[d] The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark

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ABSTRACT

Although several studies have examined the relative contributions of familial and environmental risk factors for schizophrenia, few have additionally examined the predictive power on the individual level and simultaneously examined the population impact associated with a wide range of familial and environmental risk factors. The authors present rate ratios (IRR), population-attributable risks (PAR) and sex-specific cumulative incidences of the following risk factors: parental history of mental illness, urban place of birth, advanced paternal age, parental loss and immigration status. We established a population-based cohort of 2,486,646 million persons born in Denmark between 1 January 1955 and 31 December 1993 using Danish registers. We found that PAR associated with urban birth was 11.73%; PAR associated with one, respectively 2, parent(s) with schizophrenia was 2.67% and 0.12%. PAR associated with second-generation immigration was 0.70%. Highest cumulative incidence (CI = 20.23%; 95% CI = 18.10–22.62) was found in male offspring of 2 parents with schizophrenia. Cumulative incidences for male offspring or female offspring of a parent with schizophrenia were 9.53% (95% CI = 7.71–11.79), and 4.89%, (95% CI 4.50–5.31). The study showed that risk factors with highest predictive power on the individual level have a relatively low population impact. The challenge in future studies with direct genetic data is to examine gene-environmental interactions that can move research beyond current approaches and seek to achieve higher predictive power on the individual level and higher population impact.

1. Introduction

Evidence from family, twin and adoptive studies suggest that genetic transmission accounts for most of the familial aggregation of schizophrenia (Kendler and Diehl, 1993). Registry-based epidemiologic research supports that the risk of schizophrenia is associated not only with a family history of schizophrenia (Gottesman et al., 2010) but also with other categories of mental disorders in first-degree relatives (Dean et al., 2010; Mortensen et al., 2010). In addition to a family history of mental illness, large-scale epidemiologic studies have identified a wide range of risk factors (for a review see Matheson et al. (2011)), including urban birth (Pedersen and Mortensen, 2001; Pedersen, 2006; Pedersen and Mortensen, 2006), advancing paternal age (El-Saadi et al., 2004; Miller et al., 2011; Petersen et al., 2011), migrant background (Weiser et al., 2008; Cantor-Graae and Pedersen, 2013), and parental loss (Granville-Grossman, 1966; Laursen et al., 2007).

Genetic and environmental factors are associated with psychosis risk, but the latter present more tangible markers for prevention (Kirkbride et al., 2010). In this context, relatively little attention has been given to the question of the magnitude of the population impact associated with a wide range of (genetic and environmental) risk factors for schizophrenia. Reporting on the power to predict risk on an individual level is important for preventive research as is the knowledge of the feasibility of individual screening and intervention in relation to severe mental illness (Kirkbride and Jones, 2011). While the importance of fully elucidating the likely multifactorial, multilevel, polygenetic and eco-epidemiologic basis of schizophrenia needs to be stressed, it is of added importance to provide empirical data on epidemiological associations from large-scale comprehensive studies. These continued research efforts may in turn provide important new clues to the risk architecture of schizophrenia. In this context, epidemiologic measures such as the population attributable risk (PAR) and cumulative incidences (CI) are important to the researcher, for instance when considering whether risk factors with high predictive power on the individual level have high, modest or low population impact. In an attempt to document on the population impact of familial and environmental risk factors for schizophrenia, we initiated a register-based investigation in

* Corresponding author at: Mental Health Centre Copenhagen, Bispebjerg Bakke 23, DK 2400 NV, Copenhagen, Denmark. Tel.: +45 38647441; fax: +45 3864.
E-mail address: holger.jelling.soerensen@regionh.dk (H.J. Sørensen).

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a single large sample in order to examine familial and environmental risk factors for schizophrenia jointly. Furthermore, we examined sex-specific lifetime absolute risks of these factors, as well as the relative risks (IRR) and the population attributable risks (PAR). The following risk factors could be jointly examined in our study: parental history of mental illness, urban place of birth, advanced paternal age, parental loss and immigration status.

2. Methods

2.1. Study population

We used data from the Danish Civil Registration System (CRS) to obtain information on Danish people and their parents. The register was established in 1968, where all people alive and living in Denmark were registered. Among many other variables, it includes information on personal identification number, sex, date of birth, continuously updated information on vital status, and personal identification number of parents. The personal identification number is used in all national registers enabling accurate linkage between registers. Our study population included all persons born in Denmark between 1 January 1955 and 31 December 1993, who were alive at their 15th birthday, and where information on maternal identity was available (2,486,646 million people).

2.2. Assessment of schizophrenia and mental illness in parents

The study population and their mothers and fathers were linked with the Danish Psychiatric Central Register (Munk-Jorgensen and Mortensen, 1997), which was computerized in 1969. The Danish Psychiatric Central Register contains data on all admissions to Danish psychiatric in-patient facilities, and, from 1995, information on outpatient visits to psychiatric departments was included in the register. At present the register includes data on approximately 720,000 persons and 3.2 million contacts. From 1969 to 1993, the diagnostic system used was the Danish modification of International Classification of Diseases, 8th revision (ICD-8) (WHO, 1967), and, from 1994, the diagnostic system used was the International Classification of Diseases, 10th revision (ICD-10) (WHO, 1992). Cohort members were classified as cases if they had been admitted to a psychiatric hospital or had been in outpatient care with a diagnosis of schizophrenia (ICD-8 code 295 or ICD-10 code F20). Date of onset was defined as first day of first contact (in- or outpatient) with a diagnosis of schizophrenia. Parents were categorized hierarchically with a history of schizophrenia, schizophrenia-like psychoses, or other mental disorders (any ICD-8 or ICD-10 diagnosis), respectively, if they had been admitted to a psychiatric hospital or in outpatient care with one of these diagnoses. If both parents suffered from different disorders, only the disorder with the highest hierarchy was recorded.

2.3. Assessment of exposures

Municipalities in Denmark were classified according to degree of urbanization by Statistics Denmark (Pedersen et al., 2006): capital, capital suburb, provincial city, provincial town, or rural areas, which have been used in previous studies. Maternal and paternal age at birth was subdivided into 5 and 6 categories, respectively, as in the previous studies. Information on parental loss was obtained from the Danish Civil Registration System. Parental origin was defined as follows: second-generation immigrants by both parents (mother and father born abroad), second-generation immigrants by mother (mother born abroad), second-generation immigrants by father (father born abroad), native Danes (both parents born in Denmark), as previously (Cantor-Graae and Pedersen, 2007).

2.4. Statistical analyses

A total of 2,486,646 people born in Denmark 1955–1993 were followed from their 15th birthday until onset of schizophrenia, death, emigration from Denmark, or 30 June 2009, whichever came first. The relative risk of schizophrenia was estimated by Poisson regression. All relative risks were adjusted for calendar year, age and its interaction with sex. In addition we adjusted for a slight change in the age and sex-specific incidence during the study period. As Cox regression is very computer intensive for large studies, we used Poisson regression as an approximation.

Age, calendar year, history of mental illness in parents and parental loss were treated as time-dependent variables, whereas all other variables were considered time independent. Age was categorized in 1-year intervals from age 15–19, in two-year intervals from 20 to 29, and in 5-year intervals thereafter. Calendar years were categorized as 1970–1972 and in 1-year periods thereafter. P values were based on likelihood ratio tests.

The cumulative incidences were calculated as the percentages of persons in the population who had developed schizophrenia before a given age, taking into account that people may die or migrate before the onset of schizophrenia. When calculating the cumulative incidences, history of mental illness in parents and parental loss were treated as fixed variables evaluated at the time of the 15th birthday. These analyses were made for each sex.

The population-attributable risk (the fraction of the total number of cases in the population that would not have occurred if all people had the same incidence rate as persons in the reference group) was estimated as described by Bruzzi et al. (1985).

3. Results

3.1. Incidence rates, relative risks and population-attributable risk

Among the 2,486,646 people born in Denmark between the years 1955–1993, a total of 17,389 were registered with schizophrenia during the 50,281,105 person-years of follow-up (overall incidence rate of 3.46 per 10,000 person-years at risk). There were 3420 persons with schizophrenia and a parental history of mental illness, 548 with schizophrenia and one parent with schizophrenia, and 5 persons with schizophrenia where both parents also had received the same diagnosis. A total of 1558 persons with schizophrenia had second-generation immigration background. Table 1 shows the crude and adjusted IRR's and PAR's according to parental history of mental illness, place of birth, maternal age, paternal age, maternal loss, paternal loss and immigration status. Estimates in the first adjustment were adjusted for calendar year, age and its interaction with sex, whereas estimates in the second adjustment were also adjusted for all other variables in the table. We found that the effects of most risk factors were attenuated somewhat after mutual adjustment, but all risk factors remained highly significant. In the following we only refer to the second adjustment.

3.2. Urbanization at birth

Our results suggest that the higher the degree of urbanization at place of birth is, the higher the relative risk of schizophrenia. Using birth in a rural area as the reference, people born in the capital had a 1.80-fold increased risk of schizophrenia, and the PAR associated with birth in the capital was 11.73%, i.e. if persons born in the capital had the same risk as persons born in the rural area, then 11.73% of the cases in the total Danish population would not have occurred. The highest PAR for any of the risk factors examined in this analysis was for urban birth (11.73%). The cumulative risk (i.e. sex-specific lifetime risk of schizophrenia) relative to the degree of urbanization of birth is shown in Table 2. The effects of degree of urbanization are in the same direction for men and women, and the highest lifetime risk is 2.16%