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Fertility of first-degree relatives of patients with schizophrenia: A three generation perspective

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Abstract

We explored the fertility in three generations; fertility of parents, siblings and offspring to patients with schizophrenia, to test the hypothesis that the decreased reproductive rate in the patients is compensated by an increased rate in their first-degree relatives. A population-based national database was created by linking the Swedish Multi-Generation and Hospital Discharge Registers. To maximize follow-up time for schizophrenia and reproductive history, three birth cohorts were selected: parental generation, born 1918–1927 (n=274 464); affected generation, born 1932–1941 (n=108 502) and offspring to affected generation, born 1951–1960 (n=103 105). Ratios of estimated mean number of offspring were measured (fertility ratios), comparing the study subjects to the general population. The fertility among males with schizophrenia was decreased by over 70% (fertility ratio$_{patients/population}$=0.29, 95% CI 0.25–0.35), whereas female patients had less than half as many offspring as the general female population (fertility ratio$_{patients/population}$=0.48, 95% CI 0.42–0.55). When accounting for selection bias of larger families, no statistically significant difference was found among parents of patients with and without a diagnosis of schizophrenia. Further, the fertility among siblings of schizophrenic patients did not differ from the general population. A reduction in fertility was found among offspring to patients with schizophrenia, male offspring had 12% fewer offspring (fertility ratio$_{offspring/population}$=0.88, 95%CI 0.77–1.01), while female offspring had 6% fewer offspring (fertility ratio$_{offspring/population}$=0.94, 95% CI 0.84–1.05). In conclusion, we found reduced fertility in patients with schizophrenia and among their offspring that was not compensated by higher parental or sibling fertility.

Keywords: Schizophrenia; Fertility; Parents; Siblings; Offspring; Selection bias

1. Introduction

Patients with schizophrenia have fewer offspring compared to the general population (Haukka et al., 2003; Hilger et al., 1983; Howard et al., 2002; McGrath et al., 1999; Nanko and Moridaira, 1993; Vogel, 1979), but despite the lower rates of reproduction, the incidence of this highly heritable disorder (Sullivan et al., 2003) appears to be stable (Harrison et al., 1991; Osby et al., 2001). In an effort to explain the paradox between a lower reproduction rate and the persistence of schizophrenia, it has been suggested that reproductive rates in unaffected gene carriers are increased. The hypothesis of compensatory higher fertility in healthy relatives of patients with schizophrenia has been given support

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by studies of the fertility of parents of schizophrenia patients (Avila et al., 2001; Fananas and Bertranpetit, 1995; Roth, 1959; Srinivasan and Padmavati, 1997; Waddington and Youssef, 1996), while research on the fertility among siblings of patients with schizophrenia has failed to detect any major differences (Bassett et al., 1996; Haukka et al., 2003; McGrath et al., 1999). We are unaware of studies on the fertility in offspring to patients with schizophrenia.

To test the hypothesis that the decreased reproductive rate among patients with schizophrenia is compensated by an increased rate in their relatives, we have analysed a large national sample of patients with schizophrenia and their first-degree relatives in three generations, using a register linkage between the population-based Swedish Multi-Generation and Hospital Discharge Registers. We explored the fertility in three generations; parental fertility, fertility of the siblings and fertility of the offspring to patients with schizophrenia. Selection bias of larger families was taken into account when analysing parental fertility.

2. Materials and methods

2.1. Study population

2.1.1. Data sources

The Swedish Multi-Generation Register includes children born since 1932, who are linked with their biological parents. It comprises 8.5 million children (index persons) and 11 million unique individuals (Statistics Sweden, 2005).

The Swedish Hospital Discharge Register covers details on virtually all psychiatric hospitalizations in Sweden from 1973. Dates of each hospital admission, discharge, and the main discharge diagnosis assigned by the treating physician (and up to eight secondary diagnoses if occurring) are recorded according to the International Classification of Diseases, Eighth revision (ICD-8) through 1986, Ninth Revision (ICD-9) between 1987 and 1996, and Tenth revision (ICD-10) 1997–2002. The register has a nation-wide coverage of inpatient treatment facilities and includes care in psychiatric as well as somatic hospitals (Centre for Epidemiology, 2006). The discharge diagnosis of schizophrenia has been validated and few false positive cases were reported (Dalman et al., 2002; Ekholm et al., 2005; Kristjansson et al., 1987).

A population-based database was created by linking the Multi-Generation Register (where data on offspring were available through 2002) and the Hospital Discharge Register (recorded through 2001), using the unique national registration number.

2.1.2. Cohorts of first-degree relatives

The fertility in three generations was analysed: parental generation ('generation I'); affected generation ('generation II'); and offspring to the affected generation ('generation III'). Because the first-degree relatives and their offspring have different likelihood of being included in our database depending on birth cohorts, we created three different cohorts for the analyses. Pedigrees of the analysed cohorts are shown in Fig. 1a–c.

2.1.2.1. Parental generation. The cohort for the analyses of fertility among parents was established by identifying all individuals born from 1918 through 1927, who were recorded as parents in the Multi-Generation Register (Fig. 1a, generation I). Offspring to the study subjects (Fig. 1a, generation II) were born from 1934 through 1976. There were two main reasons for the choice of cohort: Firstly, to ensure that all offspring were born after 1931 and thus included in the Multi-Generation Register. Secondly, to give the offspring enough time to develop schizophrenia, thereby minimizing misclassification of patients with late onset schizophrenia.

In the analysis of parental fertility, one has to consider selection bias, i.e., that families of different sizes are affected with different probabilities and cases are more likely to be found in larger families (Bytheway, 1974; Zelen, 2005). In a family without offspring, the probability of a schizophrenia diagnosis in generation II is null, and the more offspring, the higher the probability of a schizophrenia diagnosis. Thus, the relationship between schizophrenia and parental fertility is confounded by family size. Since family size was our outcome, it was not possible to control for number of offspring in the analysis. To avoid artificial over-representation of larger families, we only considered affection status of the first born child. We compared the fertility of the parents of all first-born children with and without schizophrenia. This comparison is valid, assuming that if parental fertility is affected by schizophrenia in the offspring, then this effect is the same independently of the birth-order of the offspring.

2.1.2.2. Affected generation. A cohort of individuals born from 1932 through 1941 was selected (Fig. 1b, generation II). The subjects were either patients with schizophrenia, siblings of patients with schizophrenia, or neither. The cohort was selected because generation II should have had time both to develop schizophrenia and to complete their reproductive history.