



# Analysis of risk factors for schizophrenia with two different case definitions: A nationwide register-based external validation study <sup>☆</sup>



Holger J. Sørensen <sup>a,e,\*</sup>, Janne T. Larsen <sup>b,e</sup>, Ole Mors <sup>d,e</sup>, Merete Nordentoft <sup>a,e</sup>,  
Preben B. Mortensen <sup>b,c,e</sup>, Liselotte Petersen <sup>b,e</sup>

<sup>a</sup> Psychiatric Centre Copenhagen, Capital Region of Denmark, University Hospital of Copenhagen, Bispebjerg Bakke 23, 2400 NV, Denmark

<sup>b</sup> National Centre for Register-based Research, Aarhus University, Business and Social Sciences, Aarhus, Denmark

<sup>c</sup> Centre for Integrated Register-based Research, CIRRAU, Aarhus University, Aarhus, Denmark

<sup>d</sup> Research Department P, Aarhus University Hospital, Risskov, Denmark

<sup>e</sup> The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark

## ARTICLE INFO

### Article history:

Received 9 October 2014

Received in revised form 29 December 2014

Accepted 8 January 2015

Available online 23 January 2015

### Keywords:

Schizophrenia

Case definition

External validation

Register-based studies

## ABSTRACT

Different case definitions of schizophrenia have been used in register based research. However, no previous study has externally validated two different case definitions of schizophrenia against a wide range of risk factors for schizophrenia. We investigated hazard ratios (HRs) for a wide range of risk factors for ICD-10 DCR schizophrenia using a nationwide Danish sample of 2,772,144 residents born in 1955–1997. We compared one contact only (OCO) (the case definition of schizophrenia used in Danish register based studies) with two or more contacts (TMC) (a case definition of at least 2 inpatient contacts with schizophrenia). During the follow-up, the OCO definition included 15,074 and the TMC 7562 cases; i.e. half as many. The TMC case definition appeared to select for a worse illness course. A wide range of risk factors were uniformly associated with both case definitions and only slightly higher risk estimates were found for the TMC definition. Choosing at least 2 inpatient contacts with schizophrenia (TMC) instead of the currently used case definition would result in almost similar risk estimates for many well-established risk factors. However, this would also introduce selection and include considerably fewer cases and reduce power of e.g. genetic studies based on register-diagnosed cases only.

© 2015 Elsevier B.V. All rights reserved.

## 1. Introduction

The decision on when to define a case of schizophrenia in register-based research is guided by several considerations. In Denmark, one contact to the secondary health care system with schizophrenia has been viewed as sufficient to define a case in register-based research. To increase the diagnostic validity, by minimizing false-positive diagnoses, researchers using the Swedish hospital discharge register sometimes employ a definition requiring a diagnosis of schizophrenia on two separate treatment inpatient contacts (Lichtenstein et al., 2006). However, a case definition of schizophrenia demanding two or more contacts (TMC) could lead to increased risk of selection. On the other hand, the advantage of the TMC definition is reduced heterogeneity among cases and a more homogeneous sample suited for e.g. biological studies (Fazel et al., 2009; Ripke et al., 2013; Ruderfer et al., 2014;

Purcell et al., 2014; Rees et al., 2014; Szatkiewicz et al., 2014). Conversely, the potential disadvantage of the OCO (one case only) definition used in Denmark is a higher risk of false-positive diagnoses. There has been several reports (Dalman et al., 2002; Ekholm et al., 2005; Uggerby et al., 2013) suggesting that the validity of a schizophrenia diagnosis is good in Swedish as well as in Danish nationwide registers. However, since there are no supportive diagnostic tests for schizophrenia, it may be important, when designing e.g. future genetic studies based on register-based samples only, to consider when to use alternative ascertainment or not. In large register-based studies, sample size and effects of common and well-established risk factors could potentially depend on the case definition of schizophrenia. To study this further, we here examine the TMC definition versus the OCO definition in an external validation study. We decided to use well-established risk factors for schizophrenia as external validators as suggested previously (Robins and Guze, 1970). These included family history of mental illness (Mortensen et al., 1999), urban place of birth (Pedersen and Mortensen, 2001), unknown parent status (Mortensen et al., 1999), advanced paternal age (Sorensen et al., 2014; McGrath et al., 2014), early parental loss (Sorensen et al., 2014), second generation immigration status (Sorensen et al., 2014), low birth weight (Abel et al., 2010), short

<sup>☆</sup> Presented at The 4th Biennial Schizophrenia International Research Society Conference, 5–9 April 2014 in Florence, Italy.

\* Corresponding author at: Mental Health Centre Copenhagen, Bispebjerg Bakke 23, 13A, DK 2400 NV, Copenhagen, Denmark.

E-mail address: [holger.jelling.soerensen@regionh.dk](mailto:holger.jelling.soerensen@regionh.dk) (H.J. Sørensen).

gestational age (Byrne et al., 2007; Nosarti et al., 2012), obstetric complications (Cannon et al., 2002), birth order (Kemppainen et al., 2001; Pedersen and Mortensen, 2004), and Apgar score (Clarke et al., 2011).

## 2. Materials and methods

### 2.1. Study population and case definitions

We used data from the Danish Civil Registration System (CRS) (Pedersen et al., 2006) which was established in 1968 to obtain information on all residents alive and living in Denmark. 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 2,772,144 people born in Denmark in 1955–1997 and followed in the period 01.01.1995 until onset of schizophrenia, death, emigration from Denmark, or 31 December 2012. The study population and their mothers, fathers and full and half siblings were linked with the Danish Psychiatric Central Register (DPCR), (Mors et al., 2011) which was computerized in 1969. DPCR 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. From 1969 to 1993, the diagnostic system used was the Danish modification of the International Classification of Diseases, 8th revision (ICD8) (WHO, 1967), and, from 1994, the International Classification of Diseases, 10th revision, Diagnostic criteria for research (ICD-10-DCR). A diagnosis of schizophrenia was defined as ICD-10-DCR F20.

We compared the conventional Danish register-based case definition of schizophrenia (OCO) with the TMC case definition. OCO defines a case of schizophrenia after the first diagnosis of schizophrenia at an outpatient or inpatient contact to the secondary health care system. TMC is defined as at least 2 diagnoses with schizophrenia as inpatients.

Parents and siblings were categorized hierarchically with a history of schizophrenia (ICD-8: 295; ICD-10-DCR: F20), or other mental disorders (any ICD-8 or ICD-10-DCR diagnosis), respectively, if they had been admitted to a psychiatric hospital or in outpatient care with one of these diagnoses.

### 2.2. Risk factors

Statistics Denmark provides data on municipalities in Denmark. We used a classification according to degree of urbanization (capital, capital suburb, provincial city, provincial town, or rural areas). Maternal and paternal age at birth was subdivided into 5 and 6 categories, respectively. Information on parental loss was obtained from the Danish Civil Registration System. Immigration status was defined as the number of parents born outside Denmark (0, 1, and 2). Second generation immigration status was defined as previously (Cantor-Graae and Pedersen, 2007). Apgar score, birth defects, gestational age, birth order and birth weight were obtained from the Medical Birth Registry. Information on maternal and paternal income, highest completed level of education and occupation the year the child turned 15 was obtained from Statistics Denmark.

### 2.3. Statistical analyses

The hazard ratio (HR) of schizophrenia according to both case definitions was estimated by Cox regression. All estimates are adjusted for calendar time as a time-dependent variable, for age in the nonparametric part of the Cox model, and for sex by means of separate underlying hazard functions. Calendar year, history of mental illness in parents, siblings and half-siblings were treated as time-dependent variables, whereas all other variables were considered time independent. Parental age was categorized as 12–19, and in 5-year intervals from age 20 and

until 35 or 45, respectively. Calendar years were categorized as 1995–1999, 2000–2004 and 2005–2012. P values were based on likelihood ratio tests. We calculated the annual mortality rate (per 1000 person-years) since the date when caseness criteria were first met after adjustment for calendar time (as a time-dependent variable), age and sex.

## 3. Results

The OCO case definition identified 15,074 individuals as cases and the TMC case definition captured 7562 (50%) of these cases. As shown in Table 1, TMC was associated with a higher mortality after adjustment for covariates including age and sex. The age and sex-adjusted annual mortality rate was significantly higher 1 year after the date at which the schizophrenia definition was met. Furthermore, the mortality rate continued to be higher during a 5 year observational period.

Table 2 shows the HRs (and 95% CI's) associated with a range of risk factors according to the OCO or TMC case definition. Generally, effects of all of these risk factors were uniform regardless of case definition. Stronger risk estimates of family history of schizophrenia were found for the TMC definition as compared to the OCO definition. More or less similar patterns were found for advanced paternal age, parental loss, urban birth and second-generation immigration status, birth weight, gestational age, Apgar score, birth defects, parental educational attainment and birth order.

## 4. Discussion

The main findings were more or less uniform risk estimates for most of the studied risk factors regardless of case definition. Trends were in the direction of similar or slightly higher risk estimates for the TMC. The TMC definition included fewer cases. Given the need for very large samples in future searches for identification of genetic variation associated with schizophrenia, i.e. in studies where size matters, it may be important to incorporate these considerations about case definitions of schizophrenia in register-based research.

The dramatic reduction from 15,074 cases with the OCO definition to 7562 cases with the TMC definition should be interpreted with caution. It is probably the result of a combination of selection and truncation at the end of the study period. There could be artificial reasons (truncation) for not having a second treatment contact counted in this analysis. We would expect cases that become incident near the end of the study period to have the highest probability for right truncation bias. Therefore, the overlap of only 50% of the OCO and TMC definitions is probably a minimum estimate. Although, it is plausible that the TMC definition selects for more chronicity, poorer treatment response and higher risk of premature mortality, it is difficult with the current register-based design to measure the extent to which these selection forces have been in place.

**Table 1**

Descriptive characteristics of cases with schizophrenia according to a definition of schizophrenia requiring “one contact only” (OCO) or at least 2 inpatient contacts with schizophrenia (TMC).

	OCO	TMC
Males N (% of total)	9174 (61%)	4542 (60%)
Age, years (mean and SD) at the time when caseness criteria were first met	28.87 (8.71)	30.31 (8.73)
Annual mortality rate (per 1000 person-years) since the date when caseness criteria were first met		
1st	9.59 (8.12–11.32)	16.08 (13.40–19.29)
2nd	10.07 (8.49–11.93)	10.78 (8.54–13.60)
3rd	7.36 (5.98–9.06)	11.28 (8.89–14.31)
4th	7.24 (5.82–9.02)	9.78 (7.49–12.77)
5th	7.05 (5.58–8.91)	11.40 (8.80–14.78)

متن کامل مقاله

دریافت فوری ←

**ISI**Articles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات