Schizophrenia Research 147 (2013) 140–146

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Schizophrenia susceptibility and age of diagnosis — A frailty approach

Elisabeth Svensson [a,b,*], Maria Rogvin [c], Christina M. Hultman [d], Ted Reichborn-Kjennerud [a,e], Sven Sandin [d], Tron A. Moger [c,f]

[a] Division of Mental Health, Norwegian Institute of Public Health, Norway
[b] Department Clinical Epidemiology, Aarhus University, Denmark
[c] Department of Health Economics and Health Management, Institute of Health and Society, University of Oslo, Norway
[d] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden
[e] Institute of Psychiatry, University of Oslo, Norway
[f] Department of Biostatistics, Institute of Basal Medical Sciences, University of Oslo, Norway

ARTICLE INFO

Article history:
Received 16 November 2012
Received in revised form 11 February 2013
Accepted 5 March 2013
Available online 27 March 2013

Keywords:
Age factors
Genetic predisposition to disease/epidemiology
Incidence
Risk factors
Schizophrenia
Susceptibility
Sweden

ABSTRACT

Background: Using a frailty model approach, we aim to evaluate the effect of early-life risk factors on susceptibility and age at diagnosis of schizophrenia. We assume paternal age and familial schizophrenia influence the susceptibility, while these and several early risk factors influence the age of diagnosis.
Method: Schizophrenia incidence data were derived from the population-based Swedish Patient Registry; including individuals aged 18 to 45 years, diagnosed between 1974 and 2008. Data were analyzed by a frailty model, a random effects model in survival analysis, using a compound Poisson model.
Results: 15,340 incident schizophrenia cases were included. For individuals without familial schizophrenia, a protective effect was seen across most ages of diagnosis for females, low paternal age, born in rural areas, and being born in later cohorts. For individuals with familial schizophrenia, a protective effect is found for females diagnosed between ages 18 and 30 years, corresponding values were 18–25 years for low paternal age. Being born in rural areas and in the last birth cohort was protective for all. The estimated proportion of susceptible was 5% for those without familial schizophrenia and 18% for individuals with familial schizophrenia. There was no statistically significant effect of paternal age on the proportion of susceptible.
Discussion: To our knowledge, this is the first regression modeling of time to schizophrenia diagnosis allowing for a non-susceptible fraction of the population, including age dependent modeling of covariate effects and an interaction. Applying frailty model to schizophrenia provide etiological clues, elucidating patterns of susceptibility and age-at-diagnosis for which early-life factors are of importance.

1. Introduction

One important epidemiological feature of schizophrenia is that the age-specific incidence curve increases until it reaches its highest point in the mid-20s, then declines (Suvisaari et al., 1999; Osby et al., 2001; Laursen et al., 2007). A frailty model describes such a downturn as the population effect of mixing two sub-groups: one highly susceptible with high risk, and perhaps early onset, and one non-susceptible, carrying almost no risk. By applying a frailty model to schizophrenia, we aim to further advance the understanding of the etiology of this complex disorder. Previously, such model has successfully elucidated the etiology of other complex disorders, such as for testis cancer (Aalen and Tretli, 1999; Moger et al., 2004) and colorectal cancer (Svensson et al., 2006).

As a consequence of the interplay between genetic background (Sullivan et al., 2003) and environmental exposures occurring early in life (Murray and Lewis, 1987), only a minority of the population is susceptible (or frail) to the disorder while the remainder of the population has almost no risk of disease. There are several examples of genetic factors conferring increased susceptibility in schizophrenia(Owen, 2012): individuals with familial schizophrenia have a ten-fold higher risk (Mortensen et al., 1999), and GWAS studies have found a number of common gene variants (SNPs) associated with increased risk (The International Schizophrenia Consortium, 2008; Lee et al., 2012). Additionally, it is hypothesized that the association between advancing paternal age and schizophrenia can be explained by a higher number of rare de novo mutations in paternal germ cells (Malaspina, 2001; Kong et al., 2012), but the direct evidence is lacking (Petersen et al., 2011). Based on the proposed genetic component of these factors, we include them in the frailty distribution, allowing them to influence the proportion of susceptible at birth. This enables us to test whether they influence susceptibility, and also enables us to examine an interaction effect, allowing the effect of the other covariates to be different, depending on whether familial schizophrenia or high paternal age is present or not. Several early-life risk factors, for example place of birth,

* Corresponding author at: Division of Mental Health, Norwegian Institute of Public Health, P.O. Box 4404, Nydalen, 0403 Oslo, Norway. Tel.: +45 29883626.
E-mail address: elisabeth.svensson@dce.au.dk (E. Svensson).

0920-9964/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.schres.2013.03.004

are also found to be associated with schizophrenia, especially in the group with familial schizophrenia (Mortensen et al., 1999; Tandon et al., 2008). However, the majority of individuals exposed to environmental factors do not develop schizophrenia; therefore, these early-life risk factors are assumed to influence the part of the model describing baseline risk and age of schizophrenia diagnosis given susceptibility (van Os et al., 2010; Svensson et al., 2012).

Frailty models have previously only been applied to schizophrenia incidence in one study from Finland which included schizophrenia incidence rates over 22 years, including gender and birth cohorts as covariates (Haukka et al., 2003). In the present investigation, we aim to extend the scope of this study. By using a frailty approach, we further evaluate the influence of early-life risk factors on susceptibility and age at diagnosis of schizophrenia. The analysis will be based on incidence rates over a 35 year period in Sweden. Covariates, such as place and time of birth, paternal age, first degree relatives with schizophrenia, are added to the model to examine the extent to which these factors can explain some of the unexplained heterogeneity in risk (Aalen and Tretli, 1999; Haukka et al., 2003; Svensson et al., 2006). To our knowledge, this is the first regression modeling of time to schizophrenia diagnosis allowing for a non-susceptible fraction of the population, and including age dependent modeling of covariate effects and an interaction effect between having familial schizophrenia and the other covariates in the data.

2. Materials and methods

2.1. Material

The present study is based on a linkage of the Swedish Patient Registry, the Multigenerational Registry of Sweden and Statistics Sweden. The Swedish Hospital discharge Registry includes data on all psychiatric inpatient care in Sweden since 1973. Schizophrenia diagnoses are coded according to the 8th (→1986), 9th (1987–1996), and 10th (1997→) editions of the International Classification of Disease (ICD). Patients with schizophrenia were defined as individuals identified with inpatient hospitalizations with a discharge diagnosis of schizophrenia (ICD-8 and ICD-9 code 295 and ICD-10 codes F20, F23.1, F23.2 and F25). Latent schizophrenia (295.5, 295F and F21) was excluded. Admissions occurring before December 31, 2008, were included in the study.

The study participants were aged between 18 and 45 years and born between 1955 and 1989. The covariates included in the model were available from Swedish national registers, and chosen for being well-documented environmental indicators of risk for schizophrenia (Tandon et al., 2008): Birth cohort (1955–64, 1965–74 and 1975–89), gender (male/female), and paternal age (<40 years/>40 years), place of birth (urban/rural: Urbanicity was defined by Swedish census data. Before 1982, subjects born in communities with less than 1000 inhabitants were considered as rural. For cohorts after 1982, we used the national register from Statistics Sweden SAMS (Small Area Market Statistic) classification data since communities were reorganized), familial schizophrenia (having a sibling with schizophrenia (yes/no)), and seasonality of birth (January–April/May–December). Covariate categorization were based on literature review, except for birth cohort, which was split into two 10-year periods, and one 15 year period based on a pragmatic decision to ensure enough cases in each birth cohort (1955–64, 1965–74 and 1975–89). For advancing paternal age, the cut-off was determined based on studies reporting that this age is where the major change in risk occur (Malaspina et al., 2001; Wohl and Gorwood, 2007). Seasonality of birth and place of birth were defined following Hultman et al. (1999) and Mortensen et al. (1999), concluding that individuals born in the months of January–April and the individuals born in urban areas are of higher risk of schizophrenia (Mortensen et al., 1999). We defined familial schizophrenia as having a sibling with disease (Svensson et al., 2012). Paternal age was missing for 1.4% of the person years, while place of birth was missing for 0.7% of the person years; these observations were deleted.

2.2. Statistical methods

Frailty modeling in survival analysis is an extension of the Cox proportional hazards model where a random effect (the frailty) has a multiplicative effect on the hazard function. Hence, the hazard rate for an individual is the frailty, Z, multiplied by the baseline hazard rate, $\lambda(t)$, that is

$$h(t|Z) = Z\lambda(t).$$

Individuals with a high value of Z have a high risk of developing the disease, whereas individuals with a low value of Z are at low risk. The frailty is assumed to follow a compound Poisson distribution which naturally allows for a non-susceptible fraction of the population (for which $Z = 0$). The choice of distribution is made based on an assumption that genetic component may be present, hence, some individuals may be susceptible, while others are virtually non-susceptible, and this is captured by the model. Appendix A provides a detailed overview of the model.

Following Aalen and Tretli (1999) and Haukka et al. (2003), the baseline hazard, $\lambda(t)$ is assumed to follow a Weibull distribution with a scale parameter a and a shape parameter k with $\lambda(t) = \exp(a)t^k$. Although frequently used in cancer models (e.g. Aalen and Tretli, 1999 and references therein), the Weibull distribution is chosen here mainly out of pragmatic reasons, as it is flexible enough to allow both increasing, decreasing and stable curves as a function of time. All covariates are, given susceptibility, assumed to influence the baseline risk, a, and speed (age of schizophrenia diagnosis), k, of the disease process. Hence, they are included in the Weibull baseline hazard function, both in the scale and shape parameter. The full model has 20 parameters in total (Appendix A). We will estimate the relative risk of schizophrenia by calculating time (age) dependent hazard ratios from the model parameters.

The data were analyzed using the software package R version 2.6.0, with the R function *nlminb* used to maximize the log-likelihood function, and standard errors calculated from the Hessian matrix using the R function *optim*. Model building was ascertained using likelihood ratio tests, in addition to visual inspection of the fit of the model to the observed data. 95% confidence intervals for the proportion of susceptible and 95% pointwise confidence intervals for the hazard ratios of each covariate were based on sampling 1000 times from the estimated multivariate normal distribution of the maximum likelihood parameter estimates, and calculating the lower and upper confidence limits as the 2.5 and 97.5th percentiles for each age (Gelman and Hill, 2006). For each covariate, we present the mean hazard ratio where the average is taken over the other covariates (Haugen et al., 2009). In addition, we present hazard ratios for each covariate for individuals having a sibling with schizophrenia and individuals without a sibling with schizophrenia separately.

3. Results

Table 1 gives an overview of the cohort, and the distribution of incident schizophrenia cases for the variables. In total, there were 15,340 schizophrenia cases recorded and 64,809,251 person years at risk (that is, the sum of the length of time each individual was followed up in the study).

The observed incidence points for each covariate are shown in Fig. 1. The curves show the simple regression fit (only one covariate included in each model) from the compound Poisson frailty model. Those having a familial schizophrenia have an increased incidence of disease compared to those without. Male gender, advanced paternal age, urban place of birth and birth cohort also have higher incidence than the reference. There are smaller differences for season of birth. In