Prognosis of schizophrenia spectrum disorder may not be predetermined during early development – the Northern Finland Birth Cohort 1966

Nina Rautio [a,b,*], Juha Käkelä [a,c,d], Tanja Nordström [a,d], Jouko Miettunen [a,c,d,e], Sirkka Keinänen-Kiukaanniemi [a,b], Leena Ala-Mursula [a], Jaro Karppinen [a,d], Matti Penttilä [c,d,e], Erika Jääskeläinen [a,c,d]

[a] Center for Life Course Health Research, University of Oulu, P.O. Box 5000, 90014 Oulu, Finland
[b] Unit of Primary Health Care, Oulu University Hospital, P.O. Box 20, 90029 OYS Oulu, Finland
[c] Research Unit of Clinical Neuroscience, Department of Psychiatry, University of Oulu, P.O. Box 5000, 90014 Oulu, Finland
[d] Medical Research Center Oulu, Oulu University Hospital and University of Oulu, P.O. Box 5000, 90014 Oulu, Finland
[e] Department of Psychiatry, Oulu University Hospital, P.O. Box 20, 90029 OYS Oulu, Finland

ARTICLE INFO

ABSTRACT

Background: Little is known about whether factors during the first years of life predict later outcomes in schizophrenia spectrum disorder (SSD). As part of the Northern Finland Birth Cohort 1966, we examined if prospectively collected early parenthood-related and developmental factors predict employment and hospitalization in individuals with and without SSD.
Methods: Overall, 161 individuals with SSD and 10,116 without SSD were included in the study. Outcomes were analysed at age of 44–45 years, defining "employment" as being employed for at least 25% of working days and "hospitalization" as having psychiatric hospitalization at least once during the last two years of follow-up. Maternal age, wantedness of pregnancy, grand multiparity, parental psychoses, birth weight, birth height, age of standing up and standing and walking without support were analysed as predictors.
Results: Of the individuals with SSD, only 11.2% were employed, although 77.6% remained not hospitalized. In individuals with SSD, only young maternal age was associated with lower probability (OR 0.25, CI 0.08–0.77) of being non-hospitalized after controlling for sex and onset age of illness. Among persons without SSD, almost all parenthood-related and developmental factors were related to employment, while grand multiparity and parental psychosis were related to hospitalization after controlling for sex.
Conclusions: Only one of the early parenthood-related and developmental factors analysed in this study predicted outcome in individuals with SSD, while among those without SSD almost all factors were related to employment. Thus, prognosis of SSD does not seem to be predetermined much by early development.

© 2016 Elsevier B.V. All rights reserved.

1. Introduction

Deviances in development and environment during early years of life increase the risk of schizophrenia (Laurens et al., 2015; Matheson et al., 2011), but their effect on prognosis after the illness onset is poorly known. There are hypotheses suggesting that some risk factors for schizophrenia such as delayed development are also prognostic indicators for patients with established illness. For example Johnstone et al. (1995) stated that "the most malignant form of schizophrenia is neurodevelopmental." The more specific hypothesis was presented by Murray et al. (1992): "congenital schizophrenia is a consequence of aberrant brain development during fetal and neonatal life. Such patients show structural brain changes and cognitive impairment, and in their male predominance, early onset, and poor outcome, they reflect Kraepelin's original description of dementia praecox." Regarding the progressive neurodevelopmental hypothesis of schizophrenia (Douaud et al., 2014; Nour and Howes, 2015), one would expect that abnormal neurodevelopment would continue after the illness onset, and thus early risk factors of illness would associate also to poorer prognosis. If there would be such association, this could indicate that the prognosis of schizophrenia is programmed already during fetal period and early development.

So far, early developmental and environmental predictors of outcomes in schizophrenia have been analysed rarely, and most studies have focused on the predictors occurring later at life. For example, previous poor working history (Marwaha and Johnson, 2004), family history of psychosis (Käkelä et al., 2014), later illness onset, longer duration of illness (Marwaha et al., 2009; Ran et al., 2011) and lower economic status of the family (Ran et al., 2011) predicted poorer employment

* Corresponding author at: Center for Life Course Health Research, University of Oulu, P.O. Box 5000, 90014 Oulu, Finland.
E-mail addresses: nina.rautio@oulu.fi (N. Rautio), juha.kakela@student.oulu.fi (J. Käkelä), tanja.nordstrom@oulu.fi (T. Nordström), jouko.miettunen@oulu.fi (J. Miettunen), sirkka.keinanen-kiukaanniemi@oulu.fi (S. Keinänen-Kiukaanniemi), leena.ala-mursula@oulu.fi (L. Ala-Mursula), jaro.karppinen@oulu.fi (J. Karppinen), matti.penttila@oulu.fi (M. Penttilä), erika.jaaskelainen@oulu.fi (E. Jääskeläinen).

status. Predictors of longer or more frequent psychiatric hospital admission include higher dosages of antipsychotics, greater proportion of prior hospitalization, earlier illness onset, lower school performance (Uggerby et al., 2011), lower social function (Olfson et al., 2011) and psychiatric co-morbidity (Lang et al., 2010).

In the very few studies of early developmental and environmental predictors of outcomes in schizophrenia, these factors mostly did not predict outcomes. The history of obstetric complications was not related to hospitalizations (Smith et al., 1995). Later achievement of learning to stand or walk and becoming potty-trained were not associated with poorer outcome at 35 years (Jääskeläinen et al., 2008). Only pre-natal exposure to environmental adversities increased the risk of re-hospitalization (Levine et al., 2014) and patients born in winter have had shorter periods of psychiatric hospitalization during first admission (Rodrigo et al., 1991). Comparative studies on developmental and environmental predictors of outcomes in schizophrenia and individuals without schizophrenia, are also lacking.

The aim of this study was to examine prospectively collected early parenthood-related and developmental factors as predictors of prognosis (i.e. register-based employment and hospitalization outcomes) in schizophrenia spectrum disorder (SSD) in years after the illness onset and to compare the results with individuals without SSD. The analysed variables were same factors, such as high maternal age, unwantedness of the pregnancy, grand multiparity, parental psychosis, high weight and low height at birth, and later achievement of standing up and standing and walking without support that increased the risk of schizophrenia in this same birth cohort sample until the ages of 44 (Keskinen et al., 2013) and 46 years (Keskinen et al., 2015). We hypothesized that early parenthood-related and developmental risk factors are related to a lower level of employment and a higher level of hospitalization at mid-life among those with SSD.

2. Methods

2.1. Sample

This study is based on the NFBC 1966 study, which is a general population cohort study concerning 12,068 pregnant women and their 12,058 live-born children in 1966 in the provinces of Oulu and Lapland (Rantakallio, 1969). This study includes individuals who were alive at the age of 16 years and living in Finland (n = 11,017). By the end of the follow-up on 31 December 2011, at the age of 45, overall 84 of them denied the use of their data, 386 had died, and 270 had emigrated and thus were excluded from the study, leading to a sample of 10,277. Permission to gather data was obtained from the Ministry of Social and Health Affairs and the study design was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District.

Diagnosis of SSD was based on an individual's presence in the national register from 1982 to 2006 (i.e. schizophrenia (ICD-8 & ICD-9: 295, ICD-10: F20), schizophreniform disorder (ICD-8 & ICD-9: 2954), schizoaffective disorder (ICD-8 & ICD-9: 2957, ICD-10: F25) or delusional order (ICD-8 & ICD-9: 297 and ICD-10: F22)), as well as follow-up of at least five years since the age of illness onset. By the end of the year 2006, at the age of 40 years, 1.6% of 10,277 individuals (n = 161; 90 men and 71 women) had SSD and all the rest 10,116 persons were without SSD. The included registers were the Care Register for Health Care (CRHC; formerly the Finnish Hospital Discharge Register), Specialized Outpatient Care Register (SOCR; information available since 1998), Register on Pensions from the Finnish Centre for Pensions (FCP), and registers from the Social Insurance Institution of Finland (SII; reimbursable medicine until the end of 2005, disability pension until the end of 2000 and sick-days until the end of 1999).

Outcomes were evaluated for persons with and without SSD from 1 January 2010–31 December 2011 at the age of 44–45 years. The length of follow-up since the onset of illness among those with SSD was on average 17.5 years: 25 (15.5%) had 5–9 years follow-up, 77 (47.8%) had 10–19 years follow-up and 59 (36.6%) had 20 years or longer follow-up.

2.2. Measures of outcomes

2.2.1. Employment status

Information on disability pension and working days during the last two years at the end of the follow-up were included in the employment status. Disability pension in Finland is based on a medical certificate, it can be granted (until further notice as a full or a partial disability pension or for a temporary period as a full or partial cash rehabilitation benefit) if a person's working capacity has been reduced for at least one year (Disability Pension, 2014). Working for a limited pay is allowed. If a person had received these benefits, she/he was considered as receiving a disability pension. Because of low number of working days among those with SSD we defined subjects as 'employed' if they had been working for at least 25% of the working days (Table 1) and all the rest were considered as 'not employed'.

Data concerning disability pensions were obtained from the FCP and SII. Although the disability pensions are usually earnings-related and covered by the employer's or entrepreneur's pension provider and therefore registered in FCP (Disability Pension, 2014), individuals can obtain disability pension from the SII, if other disability pension or reimbursement does not meet a specified limit (Social Insurance Institution, 2012). In practice those persons who fell ill early and did not enter working life were registered in the SII (data available until the end of 2000), while those who had been working were found in the register of the FCP (until the end of 2011). Employment status was based on the register obtained from the FCP until 2011.

2.2.2. Hospitalization

We analysed the presence of psychiatric hospitalizations during the two years at the end of follow-up. All the treatment periods with psychiatric diagnoses in psychiatric hospitals were gathered until the end of 2011 from the CRHC.

2.2.3. Good outcome

We combined the two aforementioned outcomes to define good outcome: employment for at least 25% of the working days and no hospitalization during the last two years of follow-up.

2.3. Predictors

Early parenthood-related and developmental factors and their classifications were based on earlier literature to present factors that increase the risk of schizophrenia (Keskinen et al., 2013; Keskinen et al., 2015).

Maternal age was classified into <20, 20–35 and >35 years (Keskinen et al., 2013) and information was obtained from the population register (Miller et al., 2011).

Wantedness of pregnancy was dichotomized into wanted/mistimed and unwanted (Myhrman et al., 1996) and *grand multiparity* was classified as "no" (<6 children) and "yes" (≥6 children) (Kemppainen et al., 2000). Information was obtained from the mother's interviews

Table 1
The distribution of the working days during the last two years of follow-up in individuals with and without schizophrenia spectrum disorder (SSD).

Working days	SSD (n = 161)		Without SSD (n = 10,116)	
	n	%	n	%
<25.0%	143	88.8	2827	27.9
25.0–49.9%	5	3.1	298	2.9
50.0–74.9%	5	3.1	371	3.7
≥75.0%	8	5.0	6620	65.4