

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

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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 10116 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.

Keywords: schizophrenia, employment, hospitalization, early predictors

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 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 midlife 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 to 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

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 persons' 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.

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.

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) (Kempainen et al., 2000). Information was obtained from the mother’s interviews

conducted by nurses in antenatal clinics using questionnaires between 1965 and 1966 (Rantakallio, 1969).

Parental (maternal/paternal) psychosis was considered “yes” if one of the parents had any psychosis (i.e. ICD-8: 295-299; ICD-9: 295, 2961E, 2962E, 2963E, 2964E, 2967 and 297-299; ICD-10: F20 and F22-F29) based on the CRHC (former Finnish Hospital Discharge Register, 1972–2012), Specialized Outpatient Care Register (1998–2012), Register of Primary Health Care Visits (2011–2012), and FCP (disability pensions, 1964–2011).

Birth weight (g) measured to the nearest 100 g, was categorized into <2500 g, 2500–4500 g and >4500 g and *height at birth* (cm) into ≤ 46 cm, 47–53 cm, and ≥ 54 cm (Moilanen et al., 2010). Information was based on the delivery records between 1965 and 1966 (Rantakallio, 1969).

The age of achievement of standing up, standing up without support and walking without support was examined in months as a continuous variable (Keskinen et al., 2015) and information was gathered from regular visits to Finnish child welfare clinics (Pillas et al., 2014).

2.4. Background factors and covariates

Sex, age at the onset of SSD, mother’s education and marital status during the pregnancy were used as background variables. The onset of SSD was based on the date of beginning of the registry entry of any psychosis diagnosis (Isohanni et al., 1997; Moilanen et al., 2003). Age at the onset of SSD was classified into <20, 20–35 and >35 years based on the earlier studies (Linke et al., 2015; Nowrouzi et al., 2015). Mother’s education was classified into 0–8 and 9 years or more, and marital status to “married” and “single/divorced/widowed” and

were obtained from the interviews conducted by nurses with the help of questionnaires (Rantakallio, 1969).

2.5. Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics version 22 [SPSS, Inc., 1989, 2013]. Cross-tabulation, χ^2 -test, Fisher's exact test and *t*-test for independent samples were used to study the association of sex, age of onset of SSD and early parenthood-related and developmental factors with employment and hospitalization. Furthermore, Mann-Whitney test was used to check the results of *t*-tests, because of skewedness in some cases in continuous variables. Binary logistic regression models were conducted to study the association between early parenthood-related and developmental factors and employment and hospitalization after adjustment for sex and age of onset of SSD in individuals with SSD and after adjustment for sex in persons without SSD.

3. Results

3.1. Outcomes

Altogether, 11.2% of individuals with SSD were employed, four of them simultaneously receiving disability pension. However, 77.6% remained not hospitalized during these last two years of follow-up (Table 2). Subjects with diagnosis of schizophrenia were less often employed and more often hospitalized than subjects with other SDD diagnosis (Table 3). Persons fulfilling both criteria of being employed and not hospitalized were exactly the same persons as those employed, since all who were employed had no hospital treatments

(Table 2). Among persons without SSD, 72.1% were employed, 98.6% were not hospitalized (Table 2) and 71.7% fulfilled both criteria.

3.2. Predictors of outcomes

None of the early parenthood-related and developmental factors were associated with employment status in individuals with SSD (Tables 2 and 4). In individuals without SSD, young maternal age, parental psychosis, lower weight and height (Table 2) and later achievement of standing up, standing up without support and walking without support (Table 4) were related to lower probability of being employed after controlling for sex (Table 5). However, among those with with SSD, young maternal age was related to hospitalization (Table 2) after controlling for sex and age at the onset of illness (Table 5). Among persons without SSD, grand multiparity and parental psychosis were associated with hospitalization (Table 2) after controlling for sex (Table 5).

4. Discussion

4.1. Main results

In SSD, none of the early parenthood-related and developmental factors were associated with employment status. However, young maternal age was related to individuals' hospitalization even after controlling for sex and onset age of illness. Instead, among those without SSD family-related and developmental factors were more often related to outcomes, especially employment after controlling for sex. Based on these results, risk factors of schizophrenia may not necessarily be also prognostic factors in SSD.

Approximately 17.5 years after illness onset, only 11% of individuals with SSD were employed, yet 78% were not hospitalized during the last two years of follow-up. While we defined good outcome as being employed for at least 25% of working days but not hospitalized during the last two years of follow-up, we found that these persons were exactly the same persons who were employed.

4.2. Employment and its predictors

We did not find association between early parenthood-related and developmental factors and employment in SSD, which was opposite to those without SSD. Low rate of employment in SSD was in line with the results of previous studies showing employment rates of 4%–36% in schizophrenia (Perälä et al., 2008; Marwaha et al., 2007). However, comparison must be conducted cautiously, because of differences in measures of employment. The unemployment rate may correlate with the economy, though it is also possible that it is due to poor functioning in SSD. Compared to those without mental health problems, persons with mental health problems are more often unemployed, and this gap has widened in Europe in 2010 compared to 2006 following the onset of the economic recession (Evans-Lacko et al., 2013). Since the unemployment rate in our data is nearly 90%, poor functioning seems more reasonable explanation than the economy. In earlier study from a Finnish sample with schizophrenia cases over 30 years, the employment rate was 7% (Perälä et al., 2008). Lack of motivation, low self-esteem, stigmatization, discrimination and fear of losing financial benefits, may also affect the employment rate in schizophrenia (Bevan et al., 2013). Employers may believe that individuals with schizophrenia can only perform low-skilled jobs (Bevan et al., 2013).

4.3. Hospitalization and its predictors

Young maternal age was related to hospitalization among those with SSD, after controlling for sex and onset age of illness. A study concerning adolescents has also shown that a higher maternal age was related to improvement in the severity of schizophrenia symptoms, but this association disappeared after adjustment for sex, diagnosis age, treatment group, paternal age, baseline Positive and Negative Symptoms Scale (PANSS) and prior hospitalization (Opler et al., 2013). Instead, Ekéus et al. (2006) reported that admissions due to schizophrenia were more likely in young persons of older women at childbirth. The results of these studies are difficult to compare with our results, because of differences in the study population, study design and measures used. Young mothers are most often unmarried, have attained low educational qualifications (Boden et al., 2008) and have mainly received public assistance as their primary source of income (Larson, 2004) and this may have an effect on motherhood. Furthermore, about 30% of adolescent mothers have reported clinically high levels of stress (Larson, 2004).

Our results concerning hospitalization rate are in line with the earlier longitudinal study reporting that 25% of individuals with schizophrenia were hospitalized for psychiatric causes during the last two years of follow-up (Ganev et al., 2007). While hospitalization is a proxy measure for illness severity (relapse), it is important to notice other factors related to context (Burns, 2007), such as availability of psychiatric beds and outpatient treatment, as an example (World Health Organization 2011).

4.4. Implications

Early parenthood-related and developmental risk factors of schizophrenia (Keskinen et al., 2013; Keskinen et al., 2015) did not predict later outcomes of illness, with the exception of young maternal age. Based on our study, the prognosis of SSD may not be predetermined in early development, and this highlights even more the importance of effective, individualized treatments. Also, it could be that factors nearer the onset of SSD are more important predictors of outcomes than early life factors present years before illness onset. For example, in smaller subsamples of this same NFBC 1966 cohort, being single (Miettunen et al., 2007), more severe symptoms of the first episode of schizophrenia (Juola et al., 2013), negative symptoms (Mäkinen et al., 2010) and use of antipsychotics (Moilanen et al., 2013) were associated with poorer outcomes even after years of illness.

Earlier research has found some support for a longitudinal association between childhood motor development and progression of cognitive deficits (Kobayashi et al., 2014), thus speaking for a link between neurodevelopment and potential neuroprogression in schizophrenia (Douaud et al., 2014; Nour and Howes, 2015). Instead, any association between motor development around age 1 year, and outcomes in schizophrenia until age 35 years was not found (Jääskeläinen et al., 2008).

4.5. Strengths and limitations

The strength is that NFBC 1966 is a population-based cohort, data concerning employment and hospitalization were based on national registers, follow-up was long and we were able to study early parenthood-related and developmental factors as predictors of outcomes of SSD. Most of these variables have not been analysed as predictors of outcomes, and there are not

many samples allowing a similar long-lasting prospective study starting already prenatally and extending to midlife. The limitations include the diagnosis of SSD being based on registers, so our study does not include persons who have not received treatment. Our sample of individuals with SSD was small and we used very loose criteria when defining employment, which was not very relevant to subjects without SSD. We could not study, for example, early exposure to environmental adversities as predictors of outcomes (Levine et al., 2014), because of lack of information.

4.6. Conclusions

The early parenthood-related and developmental risk factors for schizophrenia did not predict later outcomes in SSD, with one exception. Compared to persons without SSD, persons with SSD did not show normative associations between early parenthood-related and developmental risk factors and later outcomes at midlife studied here.

Conflicts of interest

None.

Contributors

EJ and JM designed the study. TN and NR undertook the statistical analyses. NR wrote the first version of the manuscript with the help of JK. All authors contributed to and approved the final manuscript.

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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

Table 2. Background and early parenthood-related and developmental factors and their association with employment status and hospitalization at last two years of follow-up in individuals with and without schizophrenia spectrum disorders (SSD).

	SSD										Without SSD									
	Employment status					Hospitalization					Employment status					Hospitalization				
	Employed		Not employed			Non-hospitalized		Hospitalized			Employed		Not employed			Non-hospitalized		Hospitalized		
	n	%	n	%	p	n	%	n	%	p	n	%	n	%	p	n	%	n	%	p
<i>Gender</i>																				
Men	11	12.2	79	87.8	0.637 ^a	67	74.4	23	25.6	0.273 ^b	3524	69.0	1584	31.0	<0.001 ^a	5020	98.3	88	1.7	0.002
Women	7	9.9	64	90.1		58	81.7	13	18.3		3765	75.2	1243	24.8		4957	99.0	51	1.0	
<i>Age of onset of schizophrenia</i>																				
<20 years	2	7.7	24	92.3	0.002 ^b	21	80.8	5	19.2	0.474 ^b	-		-		-		-			
20–35 years	8	7.1	105	92.9		85	75.2	28	24.8											
>35 years	8	36.4	14	63.6		19	86.4	3	13.6											
<i>Maternal age</i>																				
<20 years	2	13.3	13	86.7	0.853 ^b	8	53.3	7	46.7	0.038 ^b	650	68.5	299	31.5	0.013 ^a	931	98.1	18	1.9	0.352 ^a
20–35 years	13	11.7	98	88.3		91	82.0	20	18.0		5364	72.1	2071	27.9		7337	98.7	98	1.3	
>35 years	3	8.6	32	91.4		26	74.3	9	25.7		1262	73.8	447	26.2		1686	98.7	23	1.3	
<i>Mother's marital status</i>																				

Married	17	11.2	135	88.8	1.000 ^b	120	78.9	32	21.1	0.114 ^a	7032	72.4	2684	27.6	<0.001 ^a	9589	98.7	127	1.3	0.002 ^a
Single	1	11.1	8	88.9		5	55.6	4	44.4		235	62.8	139	37.2		362	96.8	12	3.2	
<i>Mother's education</i>																				
0–8 years	10	10.5	85	89.5	0.768 ^a	72	75.8	23	24.2	0.615 ^b	4640	70.8	1917	29.2	<0.001 ^a	6457	98.5	100	1.5	0.027 ^a
≥9 years	7	12.1	51	87.9		46	79.3	12	20.7		2510	74.8	844	25.2		3321	99.0	33	1.0	
<i>Wantedness of the pregnancy</i>																				
Wanted	14	11.1	112	88.9	0.738 ^a	96	76.2	30	23.8	0.497 ^b	6304	72.4	2405	27.6	0.240 ^a	8595	98.7	114	1.3	0.616 ^a
Unwanted	2	7.1	26	92.9		23	82.1	5	17.9		807	70.7	334	29.3		1124	98.5	17	1.5	
<i>Grand multiparity</i>																				
No	15	11.1	120	88.9	1.000 ^b	106	78.5	29	21.5	0.473 ^b	6423	72.1	2484	27.9	0.703 ^a	8794	98.7	113	1.3	0.011 ^a
Yes	2	8.0	23	92.0		18	72.0	7	28.0		854	71.6	339	28.4		1167	97.8	26	2.2	
<i>Parental psychoses</i>																				
No	13	9.6	122	90.4	0.175 ^b	103	76.3	32	23.7	0.351 ^b	6868	72.6	2597	27.4	<0.001 ^a	9347	98.8	118	1.2	<0.001 ^a
Yes	5	19.2	21	80.8		22	84.6	4	15.4		421	64.7	230	35.3		630	96.8	21	3.2	
<i>Birth weight</i>																				
<2,500 g	1	12.5	7	87.5	1.000 ^b	7	87.5	1	12.5	0.656 ^a	215	64.4	119	35.6	0.006	329	98.5	5	1.5	0.346 ^b
2,500– 4,500 g	17	11.5	131	88.5		113	76.4	35	23.6		6863	72.3	2632	27.7		9362	98.6	133	1.4	
>4,500 g	0	0	5	100.0		5	100.0	0	0		202	73.5	73	26.5		274	99.6	1	0.4	

<i>Birth height</i>																				
≤ 46 cm	2	15.4	11	84.6	0.711 ^b	11	84.6	2	15.4	0.759 ^a	299	63.5	172	36.5	<0.001 ^a	461	97.9	10	2.1	0.332 ^a
47–53 cm	15	10.9	123	89.1		105	76.1	33	23.9		6522	72.2	2506	27.8		8905	98.6	123	1.4	
≥ 54 cm	0	0	8	100		7	87.5	1	12.5		409	75.9	130	24.1		533	98.9	6	1.1	

a χ^2 -test

b Fisher's Exact Test

Table 3. Employment status and hospitalization during the last two years of follow up according to different diagnosis of schizophrenia spectrum disorder (SSD).

SSD	Employment status					Hospitalization				
	Employed		Not employed		p	Non-hospitalized		Hospitalized		p
	n	%	n	%		n	%	n	%	
Schizophrenia	8	6.4	117	93.6	0.001 ^a	91	72.8	34	27.2	0.044 ^a
Schizophreniform disorder	2	66.7	1	33.3		3	100.0	0	0	
Schizoaffective disorder	4	30.8	9	69.2		13	100.0	0	0	
Delusional order	4	20.0	16	80.0		18	90.0	2	10.0	

^a Fisher's Exact Test

Table 4. Early motor developmental factors and their association with employment status and hospitalization during the last two years of follow-up [at 45–46 years of age] in individuals with and without schizophrenia spectrum disorder (SSD).

	Employment status					Hospitalization				
	Employed		Not employed		p	Non-hospitalized		Hospitalized		p
<i>Age (months) at each developmental milestone</i>	n	mean (SD)	n	mean (SD)		n	mean (SD)	n	mean (SD)	
SSD										
Standing up	9	8.2 (1.2)	69	9.0 (1.7)	0.190 ^a	64	8.8 (1.6)	14	9.2 (2.0)	0.455 ^a
Standing up without support	8	10.9 (1.3)	62	11.1 (1.4)	0.642 ^a	57	11.1(1.4)	13	11.0 (1.1)	0.802 ^a
Walking without support	9	12.3 (1.7)	65	12.8 (2.2)	0.566 ^a	57	12.7 (2.1)	17	12.7 (2.1)	0.879 ^a
Without SSD										
Standing up	3952	8.4 (1.4)	1293	8.7 (1.6)	<0.001 ^a	5182	8.5 (1.4)	63	8.4 (1.8)	0.579 ^a
Standing up without support	3780	10.5 (1.3)	1205	10.7 (1.5)	<0.001 ^a	4919	10.5 (1.4)	66	10.7 (1.8)	0.605 ^a
Walking without support	4271	11.7 (1.6)	1357	11.9 (2.0)	<0.001 ^a	5557	11.7 (1.7)	71	11.8 (2.0)	0.742 ^a

^a *t*-test for independent samples

Table 5. Binary logistic regression analyses for employment and non-hospitalization during the last two years of follow-up according to parenthood-related and developmental factors in individuals with and without schizophrenia spectrum disorder (SSD).

	SSD				Without SSD			
	Employment		Not hospitalized		Employment		Not hospitalized	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	Model 1	Model 2*	Model 1	Model 2*	Model 1	Model 2**	Model 1	Model 2**
Maternal age	-	-					-	-
20-35 years			1.0	1.0	1.0	1.0		
<20 years			0.25 (0.08-0.77)	0.27 (0.09-0.85)	0.84 (0.73-0.97)	0.84 (0.72-0.97)		
>35 years			0.64 (0.26-1.56)	0.71 (0.29-1.77)	1.09 (0.97-1.23)	1.09 (0.97-1.23)		
Grand multiparity	-	-	-	-	-	-		
No							1.0	1.0
Yes							0.58 (0.38-0.89)	0.57 (0.37-0.88)
Parental psychosis	-	-	-	-	-	-		
No					1.0	1.0	1.0	1.0
Yes					0.69 (0.59-0.82)	0.69 (0.58- 0.81)	0.38 (0.24-0.61)	0.37 (0.23-0.60)
Birth weight	-	-	-	-			-	-
2500g-4500g					1.0	1.0		

<2500 g					0.69 (0.55-0.87)	0.68 (0.54-0.85)		
>4500g					1.06 (0.81-1.39)	1.12 (0.86-1.48)		
Birth height	-	-	-	-			-	-
47-53 cm					1.0	1.0		
≤46 cm					0.67 (0.55-0.81)	0.64 (0.53-0.78)		
≥54 cm					1.21 (0.99-1.48)	1.31 (1.07-1.60)		
Standing up	-	-	-	-	0.89 (0.85-0.93)	0.88 (0.85-0.92)	-	-
Standing up without support	-	-	-	-	0.92 (0.88-0.97)	0.92 (0.88-0.96)	-	-
Walking without support	-	-	-	-	0.92 (0.89-0.95)	0.92 (0.88-0.95)	-	-

*adjusted for sex and onset age

**adjusted for sex