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Association between family history of psychiatric disorders and long-term outcome in schizophrenia – the Northern Finland Birth Cohort 1966 study

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1. Introduction

Genetic factors have a major role in the aetiology of schizophrenia, as suggested by adoption, twin and family studies (Tsuang et al., 1991). Family history of schizophrenia is considered to be the strongest risk factor for schizophrenia with a 6.6–9.9 relative risk among first-degree relatives (Mortensen et al., 2010; Lichtenstein et al., 2009). So far the studies have not been able to identify a single gene that would have a large effect on the risk of schizophrenia, and a recent genome-wide association study reported 108 schizophrenia-associated genetic loci (Ripke et al., 2014). The emerging epigenetic research provides a further interesting aspect to the matter (Shorter et al., 2015; Ibi et al., 2015).

Outcome in schizophrenia is heterogenous (Morgan et al., 2014; Lang et al., 2013), and full recovery is relatively rare, 13.5% (Jääskeläinen et al., 2013). Many patients have deficits in social and occupational functioning (Marwaha and Johnson, 2004; Warner, 2004). Unfortunately, during the last decades, the proportion of social recovery (Warner, 2004) and full recovery (Jääskeläinen et al., 2013) in schizophrenia has not increased.

The results on the association between family history of any psychiatric disorder and outcome in schizophrenia are varying. Family history of psychiatric disorders has been associated with more psychopathological symptoms at a two-year follow-up and more rehospitalizations in a five-year follow-up (Feldmann et al., 2001), higher risk of relapse, but, interestingly, slightly less severe scores of psychopathology and a better attitude towards pharmacotherapy in a one-year follow-up (Ciudad et al., 2012). On the other hand, the number of relapses in a seven-year follow-up period did not differ based on psychiatric diagnoses in relatives (Altamura et al., 2001).

The earlier literature has often considered the family history of psychosis a sign of poor outcome in schizophrenia, although there are not many studies to support this reckoning (Bromet et al., 2005; Esterberg et al., 2010; Käkälä et al., 2014). Esterberg et al. (Esterberg et al., 2010) studied specific dimensions of *clinical* outcome in a meta-analysis, stating that family history of psychosis has a small but statistically significant impact on more severe negative symptoms, and small and non-significant impact on positive symptoms. We have previously investigated the association between family history of psychosis and *occupational*, *social* and *global* (i.e. combined occupational, social and clinical) outcome in schizophrenia in a meta-analysis (Käkälä et al., 2014). According to our review, family history of psychosis has a relatively small but statistically significant association with poor long-term *occupational* and *global* outcome. However, there were quite few studies focusing on these outcomes. In particular, there were no studies that focused on *social* outcome. Thus, research on the specific outcomes in schizophrenia is needed.

It is highly important to find predictors of poor social and occupational outcomes to have a better understanding of the factors that affect the prognosis of schizophrenia. Since patients with psychiatric family history are a possible target group for intervention, it is sensible to investigate the importance of the association between family history of psychiatric disorders and outcome in schizophrenia. In the current study the outcome is investigated thoroughly including several dimensions of outcomes, i.e. social, occupational, clinical and global aspects, with long-term follow-up in a general population sample. In addition, to our knowledge this is the first study that investigates the association between family history of psychosis and social outcome in schizophrenia.

We aimed to study how family history of psychiatric disorders, and especially psychosis, affect long-term social, occupational, clinical and global outcome in schizophrenia in a longitudinal population-based cohort. Our hypothesis was that family history of psychiatric disorders, especially psychosis, is associated with poorer long-term outcome.

2. Methods

2.1. Study population

The subjects of the study were members of the Northern Finland Birth Cohort 1966 (NFBC 1966). The NFBC 1966 is a general population based sample of 12,068 pregnant women and their 12,058 children with an expected delivery date during 1966 in two northern provinces of Finland; Lapland and Oulu (Jaaskelainen et al., 2015). Altogether 10,934 of these subjects, who were living in Finland at the age of 16, gave consent for their data to be used. The Ministry of Social and Health affairs gave permission to gather the data, and the Ethical Committee of the Northern Ostrobothnian Hospital District approved the study design.

The NFBC 1996 cohort members with psychosis were identified by using the nationwide Care Register for Health Care (CRHC) and the registers of the Finnish Social Insurance Institute. The CRHC was utilized to identify the individuals who had developed psychosis until 2008. The CRHC covers all mental and general hospitals and in-patient wards at local health centres and private hospitals. To find patients who were also treated only as outpatients, the registers of the Finnish Social Insurance Institute were used to find subjects diagnosed with psychosis by the end of year 2008, i.e. subjects with sick leave or disability pension due to psychosis or entitled to reimbursable medication due to a psychotic disorder. The diagnoses of psychosis made before 1998 were validated by using hospital notes (Isohanni et al., 1997; Moilanen et al., 2003), and the diagnoses made between 1998 and 2008 relied on the register data. Based on all this information, 266 cohort members with the diagnosis of psychosis and known address were asked to participate in a psychiatric study performed in 2008-2011, approximately at the age of 43 years (Nykänen et al., 2016).

The psychiatric study included an interview that took place in 2008-2011 at the Oulu University Hospital, Oulu, Finland. The Structured Clinical Interview for DSM-IV (SCID I –interview; First et al., 2002) resulting in DSM-IV diagnoses was conducted for all participants. Based on the SCID I –interview and registers, 69 participants had schizophrenia spectrum disorder (57 schizophrenia, 2 schizophreniform, 8 schizoaffective and 2 delusional disorder). The participation flow is presented in Figure 1.

Insert “Figure 1” here

2.2. Outcome data

To assess the different aspects of outcome (i.e. social, occupational, clinical and global), we used the Strauss-Carpenter Outcome Scale, PANSS (Positive and Negative Syndrome Scale; Kay et al., 2000) and SOFAS (Social and Occupational Functioning Assessment Scale; Spitzer et al., 2000)

outcome measures, which are widely used and provide a comprehensive overview of the outcome. As a part of the interview at the age of 43 the *Strauss-Carpenter Outcome Scale* –interview (Strauss and Carpenter, 1977) was conducted, which has been established as an outcome assessment tool (Nieman et al., 2012). It includes the following questions:

1. Frequency of social contacts
2. Quality of social relationships
3. Amount of useful employment
4. Quality of work function
5. Duration of non-hospitalization
6. Absence of symptoms
7. Ability to meet own basic needs
8. Fullness of life
9. Overall level of function

The questions were grouped into different outcome categories as follows: *social outcome* (questions 1 and 2); *occupational outcome* (questions 3 and 4); *clinical outcome* (questions 5 and 6); *global outcome* (questions 1–9). Each question is scored on a five-point scale from 0 (very poor) to 4 (very good). The sum score of the questions in each category is used in the analysis. Also the *PANSS* interview was conducted at the age of 43 to measure symptoms during the previous week. The *PANSS* is used for measuring symptom severity in schizophrenia, and it includes seven questions regarding positive symptoms, seven questions regarding negative symptoms, and 16 questions regarding general psychopathology. In this study the following five symptom dimensions were analyzed: positive, negative, emotional, excitement, and disorganization (van der Gaag et al., 2006), with higher scores indicating more severe symptoms. In addition, the *SOFAS* assessment was conducted at the age of 43 to measure social aspects and capability to work. The scale is numeric from 0 to 100 with higher scores indicating better functioning in central areas of life such as social relationships and work or school.

2.3. Other variables

The used background variables (and the source of information) were as follows:

Gender. Male vs. female.

Educational level (interview at the age of 43). Low: comprehensive school with a lower level of vocational education; middle: comprehensive school with a higher level of vocational education or upper secondary school with a lower level of vocational education; and high: upper secondary school with a higher level of vocational education.

Marital status (interview at the age of 43). Married/cohabiting vs. unmarried/divorced/widow.

Age of illness onset (hospital notes or register data). The age of illness onset was defined based on the onset of psychotic symptoms (hospital notes) or the date of the registry entry of

psychosis diagnosis (registers). In case of disability pension register, one year was subtracted from the age of onset due to the typical one-year period of sickness allowance before disability pension begins (Kela, 2015). The age of illness onset is a continuous variable.

Duration of illness. The age of illness onset was subtracted from the age at the interview to form the duration of illness. The duration of illness is a continuous variable.

DSM-IV diagnosis of schizophrenia (see Chapter 2.1). Schizophrenia vs. schizophreniform/schizoaffective/delusional disorder.

Remission (interview at the age of 43). The remission was defined based on the criteria by Andreasen et al. (Andreasen et al., 2005) using PANSS. The criteria for its duration were not regarded because the interview was done only once.

Social class of father at birth of the child in 1966 (questionnaire to parents). Unskilled workers vs. others.

2.4. Ascertainment of family history of psychiatric disorders

The following data sources were used to gather information regarding psychiatric diagnoses of the subjects' relatives:

1. The CRHC (available until 2012), and primary (2011–2012) and specialized (1998–2012) health care outpatient registers were used to discover the diagnoses of the subjects' *parents*.
2. The register of disability pensions of the Finnish Centre for Pensions was used to discover the diagnoses of the subjects' *parents* until 2011.
3. Two interviews, approximately at the ages of 34 years (1999–2001) and 43 years (2008–2011), were used to discover the diagnoses of the subjects' *parents* and *siblings*. During the interview, the interviewer filled in a semi-structured questionnaire made by authors. This interview included the following questions regarding first degree relatives: description of the illness (i.e. diagnose); symptoms; onset and duration of the symptoms; and treatment history. Selection of the subjects for the interview at the age of 34 is described elsewhere (Lauronen et al., 2007). The second interview process at the age of 43 is presented in chapter 2.1.

To gather information regarding the family *history of any psychiatric disorder*, all psychiatric diagnoses from the registers were included, with the exception of organic mental disorders, mental retardation, disorders of psychological development, behavioural and emotional disorders with onset usually occurring in childhood and adolescence, and unspecified mental disorders. This included the following ICD codes: ICD-8: 295-307, 7902; ICD-9: 295-298, 300-309, 312, 314; ICD-10: F1x1, F1x2, F20-F69 (where x refers to a specific substance). All psychiatric diagnoses gathered from the interviews, except organic mental disorders, were included. In practice the inclusion criteria from the interviews was fairly similar to the registers, because the interviewee

rarely reported childhood-related problems of relatives. When describing the sample these diagnoses were categorized as: psychosis, mood disorder, substance abuse disorder, and others.

To gather information regarding the family *history of psychosis*, the included ICD diagnoses from the registers were as follows: ICD-8: 295–299; ICD-9: 295, 2961E, 2962E, 2963E, 2964E, 2967, and 297–299; ICD-10: F20 and F22–F29. The psychosis diagnoses gathered from the interviews were grouped as follows: schizophrenia spectrum disorder, other non-affective psychosis, affective psychosis and unknown psychosis.

2.5. Statistical methods

Independent sample t-test and χ^2 -test were used to analyse the differences between those with and those without family history of psychiatric disorder by background variables. Mann-Whitney's U test was used to examine the associations between family history and outcomes. P-values of <0.05 were considered statistically significant. Statistical analyses were conducted with IBM SPSS Statistics version 22 (IBM corp., 2013).

2.6. Attrition analysis

In the total schizophrenia spectrum group ($n = 175$), the participants ($n = 69$; 39.4%) had a higher level of education (secondary or tertiary education 86% vs. 72%, $p = 0.042$) and were more often employed (26% vs. 11%, $p = 0.014$) and collecting a disability pension (45% vs. 26%, $p = 0.009$) than the non-participants ($n = 106$), but did not differ in respect to gender, number of hospital treatment days, register based parental family history of psychosis or family history of any psychiatric disorder. The final study sample comprised these 69 individuals with schizophrenia spectrum diagnosis.

3. Results

3.1. Characteristics of the study sample

The gender distribution of the final study sample was quite even (53.6% male). Altogether 54 individuals (78.3%) had family history of any psychiatric disorder: 21 individuals (30.4%) had psychosis, 27 individuals (39.1%) had mood disorder, 22 individuals (31.9%) had substance abuse disorder, and 42 individuals (60.9%) had other psychiatric disorders in the family. A minority (29.0%) were married or cohabiting. The average duration of illness was 16.9 years (SD 6.5; range 1.7–26.8 years). Family history had no significant association with background variables. The family history of psychiatric disorders by background variable is presented in Table 1.

Insert "Table 1" here

3.2. Association between family history of any psychiatric disorder and outcome

Individuals with family history of any psychiatric disorder had more severe symptoms in the positive (median (md) 11.0 vs. 16.0, $p = 0.046$) and emotional (md 13.0 vs. 17.5, $p = 0.041$) symptoms in PANSS. The association between family history of any psychiatric disorder and outcomes is presented in Table 2.

Insert “Table 2” here

3.3. Association between family history of psychosis and outcome

The family history of psychosis was not associated with outcomes. The association between family history of psychosis and outcomes is presented in Table 3.

Insert “Table 3” here

4. Discussion

4.1. Main findings

The family history of any psychiatric disorder was associated with a higher amount of positive and emotional symptoms. The family history of psychosis was not associated with outcomes. Overall, given the amount of tested parameters and the characteristics of the found associations, the association between family history of psychiatric illnesses and outcome seems small according to our results.

4.2. Comparison to earlier studies

According to earlier studies the family histories of any psychiatric disorder have been associated with more severe psychopathological symptoms (based on Global Assessment Scale and Brief Psychiatric Rating Scale), more frequent rehospitalisation and higher risk of relapse in schizophrenia (Feldmann et al., 2001; Ciudad et al., 2012), but there are also contradictory findings (Ciudad et al., 2012; Altamura et al., 2001). Therefore the results in the present study are not surprising.

Based on our systematic review of long-term outcomes (Käkelä et al., 2014), there are no studies that focus on the association of family history of psychosis with *social* outcome in schizophrenia, but we found three articles that studied a combined measure of *social* and *occupational* outcome (Lauronen et al., 2007; Kurihara et al., 2011; Ayesa-Arriola et al., 2013). In those three studies the family history of psychosis was not associated with combined social and occupational outcome. In the present study the social outcome was measured by using two questions (1. frequency of social contacts; 2. quality of social relationships) from the Strauss-Carpenter Outcome Scale –interview. Neither the family history of psychosis or family history of psychiatric disorders were associated with the social outcome according to our results.

4.3. Interpretation of the results

When studying family history of psychiatric disorders, the essential question is whether the found effect is a result of genetics or environment (Danese, 2006). We found an association between family history of *any psychiatric disorder* and outcome, and did not find an association between family history of *psychosis* and outcome. This result could be explained by genetic, environmental or statistical (too small sample size to show significant associations and/or significant results by chance) aspects, and therefore this study does not provide an answer to the above-mentioned essential question.

Fortunately, there is some indication that the novel research will bring clarification to this issue. In a recent study a high polygenic risk was associated with more chronic illness in schizophrenia, in terms of need of hospitalisations and severity of symptoms (Meier et al., 2016). Schizophrenia and other psychiatric disorders have been associated with epigenetic modifications in certain brain regions, and environmental factors may affect these epigenetic mechanisms resulting in altered gene expression during development and adulthood contributing to the progression of schizophrenia (Shorter et al., 2015; Ibi et al., 2015), which provides an interesting aspect to the pathophysiology and prognosis of the disease. There is evidence that among those with parental psychotic disorder there is broad-based risk of psychiatric disorder, rather than a one-to-one match of parental psychosis to offspring psychosis. For example, when parent has schizophrenia, the rate of offspring's any mental disorder is 0.47, the rate of depression is 0.13, and the rate of schizophrenia is 0.12, and when parent has a bipolar disorder or depression, the rate of offspring's schizophrenia is 0.04 (Rasic et al., 2014). In a genome-wide analysis a genetic connection was proposed for autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). This transdiagnostic risk may affect also outcome, and studying the association between outcome and family history of each psychiatric disorder could provide interesting results. The fact that in the current study family history of *any psychiatric disorder* was stronger predictor of outcome than family history of *psychosis*, may be due to this transdiagnostic risk.

Several copy number variants have been identified that associate with the risk of schizophrenia (The International Schizophrenia Consortium, 2008), and more recently rare loss-of-function variants have been identified from a whole-exome sequencing study (Singh et al., 2016). On the other hand, the risk of psychosis has been partly explained by polygenic background (Agerbo et al., 2015).

Family history of psychosis is often considered to be a strong risk factor for schizophrenia, such as a 10-fold increased risk among first-degree relatives (Cannon and Jones, 1996). However, according to recent meta-analysis (Macbeth et al., 2015), there is an overall effect of OR = 5.82 (95% CI 3.15–10.77) for the association between parental schizophrenia and offspring schizophrenia spectrum disorder. This gives indication that the genetic connection may not be as high as previously thought. Although, the OR also depends on the risk of schizophrenia in the comparison group, which affects the comparison of the results between studies. Also, based on our (Käkelä et al., 2014; Juola et al., 2013) and studies of other groups (Esterberg et al., 2010), family history of psychosis may not be such a strong predictor of outcome of schizophrenia as earlier considered.

Although the early phase of development has been shown to affect the risk of schizophrenia, also in the current birth cohort (Keskinen et al., 2015), development at the age of one did not associate to outcome (Jääskeläinen et al., 2008). It is possible that factors nearer to the onset of schizophrenia, such as duration of untreated psychosis, onset age, substance abuse, insight, treatment adherence, working history, economic status of family, family environment and lower school performance, are more important predictors of outcomes of schizophrenia (Marwaha and Johnson, 2004; Catty et al., 2008; Ran et al., 2011; Uggerby et al., 2011; Penttilä et al., 2014; DeLisi, 1992; McGlashan, 1986; Large et al., 2014; Giusti et al., 2015; Peuskens et al., 2010). According to one study, among subjects with a family history of serious mental illness, childhood neglect significantly raises the risk for negative symptoms of schizophrenia (Gallagher et al., 2016).

Consequently, the complex interaction of genetics and environment may play a major role in the outcome of schizophrenia (Smeets et al., 2015), and family history alone may not be a substantial factor.

4.4. Strengths and limitations

The study sample is derived from a longitudinal general population-based cohort study with high coverage and reliable data collection sources and is thus representative. The follow-up time (average 16.9 years) was fairly long and allowed measurement of symptomology and outcome from onset until the age of 43. The outcome was measured by using three different tools (Strauss-Carpenter Outcome Scale, PANSS and SOFAS), thus giving a relatively comprehensive perception regarding the matter. The information regarding the diagnoses of the subjects' relatives were collected from several different sources, thus providing comprehensive representation of the family history of psychiatric illnesses, although reliability of the diagnoses gathered during interviews can be debated.

The sample size was quite satisfactory when compared to previous related studies, but the small number of individuals with family history of psychosis ($n = 21$) leaves a possibility for type II error (lack of study power to show significant associations), and there were several tested parameters leaving a possibility for type I error (significant results by chance). The participants had a higher level of education and were more often employed than the non-participants, and therefore may represent persons with less severe schizophrenia, and thus may not be comparable to clinical studies with more severe illness course. However, the participants and non-participants did not differ in respect to gender, number of hospital treatment days, register based parental family history of psychosis or family history of any psychiatric disorder.

4.5. Conclusions

Family history of psychiatric disorders has a small association with outcome in schizophrenia. Despite family history of psychosis being a strong risk factor for schizophrenia, after years of illness it does not seem to affect outcome.

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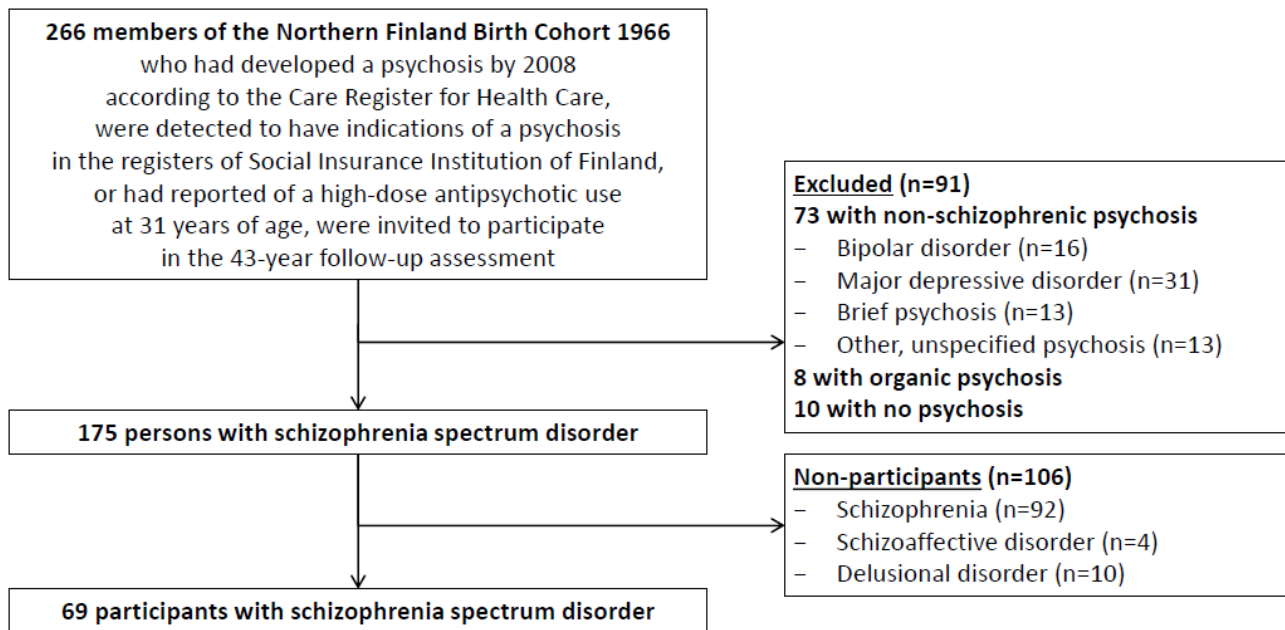


Fig.1. Flowchart of participation of the individuals.

Table 1

Family history of psychiatric disorders by background variable.

	<u>Family history of psychosis</u>			<u>Family history of any psychiatric disorder</u>		
	No <u>n (%)</u>	Yes <u>n (%)</u>	<i>P</i> -value ^a	No <u>n (%)</u>	Yes <u>n (%)</u>	<i>P</i> -value ^a
Gender			0.508			0.084
Male	27 (73)	10 (27)		11 (30)	26 (70)	
Female	21 (66)	11 (34)		4 (13)	28 (87)	
Father's social class			0.096			0.729
Low	38 (75)	13 (25)		11 (22)	40 (78)	
High	9 (53)	8 (47)		3 (18)	14 (82)	
Educational level			0.380			0.279
Low	26 (65)	14 (35)		7 (18)	33 (82)	
Middle/high	21 (75)	7 (25)		8 (29)	20 (71)	
Marital status			0.960			0.823
Married/cohabiting	14 (70)	6 (30)		4 (20)	16 (80)	
Unmarried/ divorced/widow	34 (69)	15 (31)		11 (22)	38 (78)	
Schizophrenia diagnosis			0.352			0.639
Schizophrenia	41 (72)	16 (28)		13 (23)	44 (77)	
Schizophreniform/ schizoaffective/ delusional	7 (58)	5 (42)		2 (17)	10 (83)	
Remission ^b			0.415			0.963
No	33 (73)	12 (27)		10 (22)	35 (78)	
Yes	14 (64)	8 (36)		5 (23)	17 (77)	
	<u>mean (sd)</u>	<u>mean (sd)</u>		<u>mean (sd)</u>	<u>mean (sd)</u>	
Age of illness onset	27.3 (7.0)	24.1 (6.0)	0.058	27.9 (8.0)	25.9 (6.4)	0.300
Duration of illness	15.9 (6.5)	19.1 (5.9)	0.077	15.6 (7.7)	17.3 (6.1)	0.370

^a Statistical significance based on chi-square test and independent sample t-test as appropriate.^b The remission was defined based on the criteria by Andreasen et al. (2005). The duration criteria was not regarded because the PANSS was studied only once.

Table 2

Family history of any psychiatric disorder by outcome measure.

	Family history of any psychiatric disorder		<i>U</i> ^b	<i>P</i> -value ^c
	No (n=15) median (IQR) ^a	Yes (n=52) median (IQR)		
Strauss-Carpenter ^d				
Social outcome	6.0 (4.0-7.0)	5.0 (7.0-8.0)	288.5	0.138
Occupational outcome	4.0 (2.0-7.0)	3.0 (0.0-6.0)	219.0	0.329
Clinical outcome	6.5 (4.0-8.0)	6.5 (5.0-7.0)	344.5	0.927
Global outcome	26.0 (18.0-30.0)	23.5 (17.0-29.0)	357.0	0.484
Symptom dimensions of PANSS ^e				
Negative	19.0 (10.0-28.0)	15.5 (11.0-26.8)	369.5	0.757
Positive	11.0 (8.0-18.0)	16.0 (11.0-20.0)	257.5	0.046
Disorganized	18.0 (11.0-33.0)	21.5 (15.3-34.5)	326.0	0.335
Excitement	14.0 (11.0-20.0)	14.0 (11.0-18.0)	384.0	0.928
Emotional	13.0 (12.0-18.0)	17.5 (13.0-25.0)	254.5	0.041
SOFAS ^f	50.0 (38.8-80.0)	45.0 (35.0-63.3)	295.0	0.279

^a IQR = interquartile range.^b Mann-Whitney U test.^c Statistical significance based on Mann-Whitney U test.^d Strauss-Carpenter Outcome Scale –interview (Strauss and Carpenter, 1977) (higher scores indicating better outcome).^e Positive and Negative Syndrome Scale, factors based on van der Gaag et al. (2006) (higher scores indicating more severe symptoms).^f Social and Occupational Functioning Assessment Scale (Spitzer et al., 2000) (higher scores indicating better functioning).Statistically significant *p*-values in **bold**.

Table 3

Family history of psychosis by outcome measure.

	Family history of psychosis		<i>U</i> ^b	<i>P</i> -value ^c
	No (n=48)	Yes (n=21)		
	median (IQR) ^a	median (IQR)		
Strauss-Carpenter ^d				
Social outcome	7.0 (5.0-8.0)	7.0 (5.0-8.0)	453.5	0.925
Occupational outcome	3.0 (2.0-6.8)	3.0 (0.0-6.3)	277.0	0.381
Clinical outcome	7.0 (6.0-7.0)	6.0 (4.0-7.0)	377.5	0.354
Global outcome	24.0 (18.0-29.0)	22.0 (15.0-30.0)	482.5	0.779
Symptom dimensions of PANSS ^e				
Negative	17.0 (11.0-27.0)	15.5 (10.0-28.3)	461.0	0.902
Positive	15.0 (9.0-20.0)	13.5 (9.5-22.8)	432.5	0.607
Disorganized	23.0 (13.0-33.0)	20.0 (15.3-34.5)	440.0	0.681
Excitement	14.0 (11.0-18.0)	14.0 (10.3-20.5)	437.0	0.650
Emotional	17.0 (13.0-23.0)	15.5 (13.0-25.0)	449.0	0.773
SOFAS ^f	45.0 (36.0-63.0)	46.0 (32.0-67.0)	461.5	0.880

^a IQR = interquartile range.^b Mann-Whitney U test.^c Statistical significance based on Mann-Whitney U test.^d Strauss-Carpenter Outcome Scale –interview (Strauss and Carpenter, 1977) (higher scores indicating better outcome).^e Positive and Negative Syndrome Scale, factors based on van der Gaag et al. (2006) (higher scores indicating more severe symptoms).^f Social and Occupational Functioning Assessment Scale (Spitzer et al., 2000) (higher scores indicating better functioning).

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