Association between family history of mental disorders and outcome in psychotic disorders

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PII: S0165-1781(18)30815-1
DOI: https://doi.org/10.1016/j.psychres.2018.10.047
Reference: PSY 11823

To appear in: *Psychiatry Research*

Received date: 1 May 2018
Revised date: 17 October 2018
Accepted date: 19 October 2018

Please cite this article as: J. Käkelä , T. Nordström , M. Haapea , E. Jääskeläinen , J. Miettunen , Association between family history of mental disorders and outcome in psychotic disorders, *Psychiatry Research* (2018), doi: https://doi.org/10.1016/j.psychres.2018.10.047

Highlights

- The presence of any parental psychiatric disorder is associated with higher number of hospitalizations in psychotic disorders
- The presence of parental psychosis is not associated with outcome in psychotic disorders
- The study is based on a general population-based cohort with high coverage and reliable register data
- The results should be interpreted with caution due to small sample size

17th Oct 2018

Abstract 204 words

Manuscript 3423 words

Tables = 4

Figures = 0

Association between family history of mental disorders and outcome in psychotic disorders

Running title: **Family history and outcome in psychotic disorders**

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ABSTRACT

We investigated the association of family history of mental disorders, especially psychosis, with occupational and clinical outcome in psychotic disorders in a longitudinal population-based cohort. The Northern Finland Birth Cohort 1986 (n = 9432) was used to gather the data. In total 189 individuals with psychosis were identified by age of 28. The outcome was assessed by using register information regarding occupational activity, disability pension and hospital treatments due to psychiatric cause. Parental psychosis and any psychiatric disorder were used as predictors of outcome. The results showed that presence of any parental psychiatric disorder was associated with higher number of days spent at hospital and higher number of hospitalizations in psychotic disorders, but was not associated with occupational outcome or disability pension. The presence of parental psychosis was not associated with outcome. These findings suggest that the presence of

any psychiatric disorder among parents may increase the risk of poorer outcome in psychoses in terms of need of hospitalisations. Based on this study the presence of parental psychosis is not associated with outcome, but the result should be interpreted with caution due to the small sample size and conflict with the results of earlier studies.

Keywords: heritability, prognosis, schizophrenia

1. Introduction

Schizophrenia is a mental disorder with a heterogeneous genetic, neurobiological and environmental background (Kahn et al., 2015). Family history of schizophrenia is the most significant risk factor for schizophrenia, and a recent meta-analysis (MacBeth et al., 2015) showed an odds ratio of 5.8 for the association between parental and offspring schizophrenia.

Family environment may affect outcome in schizophrenia. For example, good family relationships increase the likelihood of a good response to antipsychotic treatment (Ezeme et al., 2016), whereas social isolation and living apart from relatives results in poorer global outcome (Harvey et al., 2007). In families with schizophrenia adverse events in childhood such as prenatal health problems, deficits in mother-infant interaction and environmental disruptions are elevated (Wan et al., 2007; Walder et al., 2014) and childhood adversities predict poorer outcome in psychosis (Kilian et al., 2017; Pruessner et al., 2018). Also genetics have been shown to affect outcome. For example, a high polygenic risk was associated with more severe symptoms and greater need for hospitalisation (Meier et al., 2016) and DRD2 gene 141C insertion increased positive symptoms (Xiao et al., 2013) in schizophrenia. Since family history of psychiatric disorders can be hypothesised to have both genetic and environmental effects, it is sensible to investigate how family history of psychiatric disorders affect outcome in psychotic disorders.

The association between family history of psychosis and outcome in schizophrenia has been studied in several original publications and two meta-analyses. In meta-analyses the family history of psychosis has been associated with more severe negative symptoms (Esterberg et al., 2010) and poorer long-term occupational and global outcome (Käkelä et al., 2014) in schizophrenia. In an older (mean age 43) birth cohort of the same region as the current study the family history of psychosis was not associated with occupational, social, clinical or global outcome in schizophrenia (Käkelä et al., 2017). Family history of schizophrenia or psychosis has been associated with more frequent or longer hospitalisation in schizophrenia in several studies (Erlenmeyer-Kimling and Nicol, 1969; McGlashan, 1986; Suvisaari et al., 1998; Dadić-Hero et al., 2013). So far the studies have focused on individuals with schizophrenia, and to our knowledge there are no studies examining all psychoses, and therefore studying all psychoses could bring new aspect to the matter. Also, previously the studies have mainly comprised of either relatively old individuals or individuals of wide age range, and therefore studying younger individuals is an interesting theme. Younger individuals are also more potential prospects for interventions.

The association between family history of any psychiatric disorder and outcome in schizophrenia has been studied in a few original publications with conflicting results (Feldmann et al., 2001; Ciudad et al., 2012; Altamura et al., 2001; Käkelä et al., 2017). Since there are only few studies regarding the association between familial any psychiatric disorder and outcome in schizophrenia or other psychoses, the topic should be studied more. There is also rationale for studying association between psychotic disorders and other mental disorders because there are phenotypical overlaps between mental disorders (Doherty and Owen, 2014), and also a genetic connection has been proposed for autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia in a genome-wide analysis (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013).

Since affecting outcome has a central role in psychiatry, it is worthwhile to investigate predictors of outcome in order to explore new ways to improve the outcome. The aim of this study was to investigate the association of family history of mental disorders, and especially psychosis, with occupational and clinical outcome in psychotic disorders in a longitudinal population-based cohort until age of 30. Our hypothesis was that family history of mental disorders, especially psychosis, is associated with poorer outcome.

2. Methods

2.1. Study population

The Northern Finland Birth Cohort 1986 (NFBC1986) comprises of individuals who had an expected date of birth between 1st of July 1985 and 30th of June 1986 in two northern provinces of Finland; Oulu and Lapland (Järvelin et al., 1993). The cohort included 99% of all births in the given time and place and included 9432 live born children. The Northern Finland has a distinguishing feature of having high prevalence of schizophrenia (1.8% compared to 0.9% in the whole country; Suvisaari et al., 2012). The Ministry of Social Affairs and Health and the Finnish Privacy Protection Agency have approved the data protection of the study. The Ethical Committee of the Northern Ostrobothnia Hospital District has approved the study design.

To find NFBC1986 cohort members with psychosis the Care Register for Health Care (CRHC; inpatient treatments until 2013), the Finnish outpatient registers (specialised care 1998-2013; primary care 2011-2013), the Social Insurance Institution (SII) registers (patients entitled to reimbursable medicines; until 2005) and the register of the Finnish Centre for Pensions (FCP; disability pensions until 2013) were being utilised (Filatova et al., 2017). Based on these registers 189 individuals with psychosis were identified for the study, which accounts for 2.0% of the cohort population. When finding cohort members with psychosis, the register information was utilised until 2013 in order to have a follow-up period of at least two years (please see Chapter 2.4).

When selecting the study subjects the following psychosis diagnoses were included: schizophrenia, persistent delusional disorders, acute and transient psychotic disorders, induced delusional disorder, schizoaffective disorders, mania with psychotic symptoms, bipolar affective disorder with psychotic symptoms, depressive disorder with psychotic symptoms, other nonorganic psychotic disorder and unspecified nonorganic psychosis, which corresponds to the ICD-10 codes F20, F22-F29, F30.2, F31.2, F31.5, F32.3 and F33.3. Hence, schizotypal disorder (F21) was not included in the psychoses.

2.2. Ascertainment of family history of mental disorders

To find information regarding the psychiatric diagnoses of the study subjects' parents the following registers were used: the CRHC (inpatient treatments 1972-2015), the Finnish outpatient registers (specialised care 1998-2015; primary care 2011-2015) and the FCP register (disability pensions 1964-2016).

Parental psychosis and parental any psychiatric disorder were used as predictors of outcome. The parental psychosis included the same ICD-10 diagnoses as with the study subjects as described previously.

The any psychiatric disorder of a parent included all non-organic mental and behavioural disorders due to psychoactive substance use, psychotic disorders, mood (affective) disorders, neurotic, stress-related and somatoform disorders, behavioural syndromes associated with physiological disturbances and physical factors, and disorders of adult personality and behaviour, which corresponds to the ICD-10 codes F1x1, F1x2 (where x refers to a specific substance) and F20-F69.

2.3. Background variables

The associations between parental mental disorders (psychosis and any psychiatric disorder) and the following background variables of the offspring (hereafter "study subject") were analysed: study subjects' gender, psychosis diagnosis, age at the onset of psychosis and length of follow-up. The information regarding background variables was received from the registers as described above (Chapter 2.2).

2.4. Outcome data

The outcome of the study subjects was assessed by using register information regarding occupational activity, disability pension and hospital treatments due to psychiatric cause. The average follow-up period was 8.8 years (range 2.1-20.7). The occupational activity was assessed by measuring the cumulative number of work days in 2014-2015 (i.e. minimum of two years after onset of illness); this information was received from the FCP register. The study subjects were divided into two classes based on work activity; those who worked less and those who worked more than 25% of working days. The information regarding disability pension at the end of 2015 (i.e. at the end of the follow-up, at the age of 29-30) was also received from the FCP register. The disability pension can be granted if an individual's ability to work has been substantially reduced for at least one year, as evaluated by a medical expert and a claims processor at the Finnish Centre for Pensions based on the medical doctor's statement, and it is therefore a fairly valid measure of occupational outcome. The psychiatric hospital treatments since the onset of psychosis were assessed using the CRHC (inpatient treatments until 2015). The number of hospital treatment days, number of treatment episodes and proportion of time spent in hospital due to any psychiatric diagnosis (since the onset of psychosis) were measured.

2.5. Statistical methods

The associations between parental mental disorders and background variables of study subjects were analysed using a chi square test and independent sample t-test as appropriate. The associations between study subjects' psychosis diagnosis (schizophrenia spectrum vs. other non-organic psychosis) and outcome were analysed using the Mann-Whitney U test and chi square test as appropriate. The associations between parental mental disorders and study subjects' outcomes were analysed using the Mann-Whitney U test and chi square test as appropriate. Descriptive statistics are presented using frequency distributions, means with standard deviations (normally distributed variables) and medians with interquartile ranges (skewed variables). P-values of <0.05 were considered statistically significant. Multivariate analyses were not performed as none of the background variables associated with parental mental disorders. Statistical analyses were conducted with IBM SPSS Statistics version 24 (IBM corp., 2016).

3. Results

3.1. Characteristics and outcome of the study sample

Of the 189 study subjects with psychosis 44 (23%) had schizophrenia, 15 (8%) had schizophreniform, schizoaffective or delusional disorder, 47 (25%) had depressive or bipolar disorder with psychotic symptoms and 83 (44%) had other psychosis. Of the 189 study subjects with psychosis 155 (83%) individuals had also another (comorbid) mental disorder. The average onset age was 21.2 years (standard deviation (sd) 4.0), and the average length of follow-up 8.8 years (sd 4.0; range 2.1-20.7). The length of follow-up was ≥5 years for 145 (77%) individuals.

Of the 189 study subjects with psychosis, altogether 88 individuals (47%) had any parental psychiatric disorder: 20 individuals (11%) had parental psychosis, 65 individuals (34%) had parental mood disorder and 34 individuals (18%) had parental substance abuse disorder. Only one (0.5%) study subject had both parents having psychosis, and 21 (11%) study subjects had both parents having any psychiatric disorder. Of the 20 study subjects who had parental psychosis, 17 (85%) individuals' parent had also another (comorbid) mental disorder. Of the 88 study subjects who had any parental mental disorder, 50 (57%) individuals' parent had comorbid mental disorder. The parental mental disorders did not associate with any of the background variables (Table 1).

Thirty six study subjects (19%) had a disability pension at the end of the follow-up (i.e. end of 2015), of which 34 individuals (94%) had disability pension due to psychiatric disorder, one individual (3%) due to neurological disorder, and one individual (3%) due to disease of the musculoskeletal system. One hundred and six study subjects (56%) did not have any work activity in 2014 and 109 study subjects (58%) did not have any work activity in 2015. After onset of psychosis, 150 study subjects (79%) had been hospitalised by the end of the follow-up due to psychiatric cause. Among the 150 hospitalised individuals, the total amount of time spent at a hospital after onset of psychosis was on average 183 days, they had spent on average 5.9% of their time at a hospital, and they had been hospitalised on average 4.9 times.

The associations between the study subjects' psychosis diagnosis (schizophrenia spectrum vs. other non-organic psychosis) and outcome is presented in Table 2. Schizophrenia spectrum diagnosis was associated with poorer outcome in terms of hospital treatments, occupational activity and disability pension.

Insert Table 1 here.

Insert Table 2 here.

3.2. Association between parental psychosis and outcome

The presence of parental psychosis was not associated with occupational outcome, disability pension or hospital treatments due to psychiatric cause (Table 3).

Insert Table 3 here.

3.3. Association between any parental psychiatric disorder and outcome

The presence of any parental psychiatric disorder was associated with higher amount of hospital treatments due to psychiatric cause. The presence of any parental psychiatric disorder was not associated with occupational outcome or disability pension (Table 4).

Insert Table 4 here.

4. Discussion

4.1. Main findings

The any parental psychiatric disorder was associated with higher number of days spent at hospital and higher number of hospitalisations after onset of psychosis, but was not associated with occupational outcome or disability pension. The parental psychosis was not associated with outcomes.

4.2. Comparison to earlier studies

According to earlier studies (please see Introduction) the family history of *psychosis* has often been associated with poorer outcome in schizophrenia, and therefore the current study is not in line with the earlier findings. One considerable explanation for this is that the current study investigates all psychoses instead of only schizophrenia, which has not been studied earlier according to our knowledge. In the current study 31% had schizophrenia spectrum disorder and 69% other psychosis. As shown in chapter 3.1 (Table 2), the study subjects with schizophrenia had significantly poorer outcome compared to other psychoses. However, in the earlier meta-analyses (Esterberg et al., 2010; Käkelä et al., 2014) roughly half of the studies did not show an association between familial psychosis and outcome, and in none of the studies family history was associated

with better outcome, and therefore the current study is not in conflict with the literature either. Interestingly, in those studies that found an association between familial psychosis and outcome, the follow-up period was on average 15.5 years, whereas it was only 8.9 years in those studies that did not find an association (Esterberg et al., 2010; Käkelä et al., 2014). In the current study the follow-up period was on average 8.8 years and therefore it is in line with this earlier finding that a study with shorter follow-up period is less likely to find a significant association.

Earlier the association between family history of *any psychiatric disorder* and outcome in schizophrenia has shown mixed results. Family history of any psychiatric disorder has been associated with more and less psychopathological symptoms (Feldmann et al., 2001; Ciudad et al., 2012), more rehospitalisations (Feldmann et al., 2001) and higher risk of relapse, but also with a better attitude towards pharmacotherapy (Ciudad et al., 2012), and in one study there was no association with number of relapses (Altamura et al., 2001). Hence, in only one study family history was associated with better outcome (Ciudad et al., 2012). According to the current study the presence of any parental psychiatric disorder may increase the need of hospitalisations, and the result is therefore in line with a previous study (Feldmann et al., 2001).

4.3. Interpretation of the results

Presence of any parental psychiatric disorder was associated with poorer outcome in psychoses in terms of need of hospitalisations. This is not necessarily due to more severe illness course, but could be explained also with learned treatment seeking behaviour in the family. The activity of family members seem to affect the help-seeking behaviour in first-episode psychosis (Fridgen et al., 2013; Okasha et al., 2016; Connor et al., 2016), but there is much less research regarding the impact of family factors on rehospitalisation. The statistical tests were done in two groups and on five outcome measures (10 individual analysis), and the significant findings barely surpassed the limit of 0.05, so the result should be considered carefully.

As stated in the Introduction, family history of psychiatric disorders can be hypothesised to have both genetic and environmental effects. The genetic connection (heritability) is stronger in schizophrenia than in other psychoses (Mortensen et al., 2010). Therefore the association between family history of mental disorders and outcome could be different in schizophrenia and other psychoses, i.e. in schizophrenia the genetic component could be stronger. This could explain why the current study did not find an association between parental psychosis and outcome in psychotic disorders in contrary to many previous studies focusing only on individuals with schizophrenia.

The results were statistically significant only between family history of any psychiatric disorder and outcome, and there was no association between family history of psychosis and outcome, similarly as in the older cohort (Käkelä et al., 2017). Most likely the genetic connection between familial psychosis and psychotic disorder of the study subject is stronger than between familial any psychiatric disorder and psychotic disorder of the study subject (Rasic et al., 2014). Therefore one explanation for the findings of the current study could be the influence of environmental effect. However, the environmental burden in families with psychosis (Wan et al., 2007; Matevosyan, 2011; Walder et al., 2014) could be even higher than in families with other mental disorders, and thus the issue is not straightforward. Those who had parental psychosis or any psychiatric disorder often had poorer outcome, but the results were statistically significant only in two tested outcomes, which raises question whether larger sample size would have showed more significant results.

Schizophrenia is a result of an interplay between genetic and environmental risk factors (Kahn et al., 2015; Smeets et al., 2015; Gallagher and Jones, 2016). There is an increasing amount of research studying the genetic influences on the risk (Agerbo et al., 2015; Shorter and Miller, 2015; Ibi and González-Maeso, 2015; Singh et al., 2016) and outcome (Meier et al., 2016) of schizophrenia. Also the connection between different types of mental disorders have been studied (Rasic et al., 2014; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Due to the marginal findings the clinical relevance of the current study is not large, which could be explained by the complex aetiology of schizophrenia in which the family history alone does not play a major role.

4.4. Strengths and limitations

This study is based on a general population-based cohort with high coverage and reliable register data. The registry-based research has significant strengths and limitations. The disability pension and work activity from the Finnish Centre for Pensions and the psychiatric hospital treatments from the Care Register for Health Care can be considered fairly good measures of outcome. There was no attrition because the outcome is based on register data. We were also able to link data from all study subjects, because individual permissions were not required. However, the registers were not created for research use. The outcome variables may have limitations regarding validity. The disability pension is not a direct measure of work ability. The work variable (number of workdays) does not describe the quality of work or performance at work. It is a limitation that the register data does not have information regarding e.g. illness severity, recovery or accurate date of illness onset (only date of diagnosis). The age of illness onset of parents was not regarded, and therefore we could not draw conclusions how the parent's illness had affected e.g. treatment seeking behaviour of the study subjects. Only public registers were used to acquire information regarding parent's mental disorders, and therefore we have missed those with visits only to private health services. Also, since not all individuals seek help for mental disorders, the "no parental psychiatric disorder" group is likely to include families where the parents have undiagnosed mental disorder.

The total sample size of 189 is satisfactory, but the small number of individuals with parental psychosis (n = 20) is a limitation, and we could not analyse the results separately based on psychosis diagnosis (i.e. schizophrenia spectrum vs. other psychoses). Power calculation was conducted regarding association between parental psychosis and outcome: the average power to detect small effect sizes (Cohen $d \geq 0.2$) was 14% ($p < 0.05$), 56% for medium effect sizes (Cohen $d \geq 0.5$) and 88% for large effect sizes (Cohen $d \geq 0.8$). We were able to analyse fairly long-term outcomes (the average follow-up period was 8.8 years). The relatively young age of the study subjects (29-30 years at the end of the follow-up in the end of 2015) is a limitation, since some individuals may not yet have completed their education yet, or may have only recently entered working life and may be unemployed due to reasons other than ability to work. On the other hand, it is also a benefit that the results are generalizable to younger patients.

4.5. Conclusions

The presence of any parental psychiatric disorder may increase the risk of poorer outcome in psychoses in terms of need of hospitalisations. The presence of parental psychosis was not

associated with outcome in psychotic disorders, but the result should be interpreted with caution due to power limitation because of the small sample size and conflict with the results of earlier studies. Based on this study there is some indication of correlation between family history of mental disorders and outcome in psychotic disorders, and this information could be valuable as a predictor of prognosis when combined with other significant information regarding the patient's background. Since affecting outcome has a central role in psychiatry, it could be beneficial to compare treatment methods (e.g. antipsychotics) between those with and without a family history of mental disorders.

Funding of the study

This study was funded by the Academy of Finland (grant numbers 278286, 268336), the Sigrid Jusélius Foundation, the Brain & Behavior Research Foundation, the North Ostrobothnia Regional Fund of the Finnish Cultural Foundation and the University of Oulu Scholarship Foundation. The funders had no role in the design or conduct of the study.

References

Agerbo, E., Sullivan, P.F., Vilhjálmsson, B.J., Pedersen, C.B., Mors, O., Børglum, A.D., et al., 2015. Polygenic Risk Score, Parental Socioeconomic Status, Family History of Psychiatric Disorders, and the Risk for Schizophrenia: A Danish Population-Based Study and Meta-analysis. JAMA Psychiatry 72 (7), 635-641. doi: 10.1001/jamapsychiatry.2015.0346.

Altamura, A.C., Bassetti, R., Sassella, F., Salvadori, D., Mundo, E., 2001. Duration of untreated psychosis as a predictor of outcome in first-episode schizophrenia: A retrospective study. Schizophrenia Research 52 (1-2), 29-36.

Ciudad, A., San, L., Bernardo, M., Olivares, J.M., Polavieja, P., Valladares, A., et al., 2012. Relapse and therapeutic interventions in a 1-year observational cohort study of nonadherent outpatients with schizophrenia. Progress in Neuro-Psychopharmacology & Biological Psychiatry 36 (2), 245-250.

Connor, C., Greenfield, S., Lester, H., Channa, S., Palmer, C., Barker, C., et al., 2016. Seeking help for first-episode psychosis: a family narrative. Early Intervention in Psychiatry 10 (4), 334-45. doi: 10.1111/eip.12177. Epub 2014 Oct 9.

Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet 381 (9875), 1371-1379. doi: 10.1016/S0140-6736(12)62129-1.

Dadić-Hero, E., Ruzić, K., Palijan, T.Z., Graovac, M., Siuc-Valković, D., Knez, R., et al., 2013. Relations between the course of illness, family history of schizophrenia and family functioning in persons with schizophrenia. Collegium Antropologicum, 37 (1), 47-55.

Doherty, J.L., Owen, M.J., 2014. Genomic insights into the overlap between psychiatric disorders: implications for research and clinical practice. Genome Med, 6 (4), 29. doi: 10.1186/gm546. eCollection 2014.

Erlenmeyer-Kimling, L., Nicol, S., 1969. Comparison of hospitalization measures in schizophrenic patients with and without a family history of schizophrenia. British Journal of Psychiatry 115, 321-34.

Esterberg, M.L., Trotman, H.D., Holtzman, C., Compton, M.T., Walker, E.F., 2010. The impact of a family history of psychosis on age-at-onset and positive and negative symptoms of schizophrenia: A meta-analysis. Schizophrenia Research 120 (1-3), 121-130.

Ezeme, M.S., Uwakwe, R., Ndukuba, A.C., Igwe, M.N., Odinka, P.C., Amadi, K., et al., 2016. Socio-demographic correlates of treatment response among patients with schizophrenia in a tertiary hospital in South-East Nigeria. African Health Sciences 16 (4), 1036-1044. doi: 10.4314/ahs.v16i4.21.

Feldmann, R., Hornung, W.P., Buchkremer, G., Arolt, V., 2001. The influence of familial loading on the course of schizophrenic symptoms and the success of psychoeducational therapy. Psychopathology 34 (4), 192-197.

Filatova, S., Marttila, R., Koivumaa-Honkanen, H., Nordström, T., Veijola, J., Mäki, P., et al., 2017. A comparison of the cumulative incidence and early risk factors for psychotic disorder in young adults in the Northern Finland Birth Cohorts 1966 and 1986. Epidemiology and Psychiatry Sciences 26 (3), 314-324. doi: 10.1017/S2045796016000123.

Fridgen, G.J., Aston, J., Gschwandtner, U., Pflueger, M., Zimmermann, R., Studerus, E., et al., 2013. Help-seeking and pathways to care in the early stages of psychosis. Social Psychiatry and Psychiatric Epidemiology 48 (7), 1033-43. doi: 10.1007/s00127-012-0628-0. Epub 2012 Dec 25.

Gallagher, B.J., Jones, B.J., 2016. Neglect and hereditary risk: Their relative contribution to schizophrenia with negative symptomatology. International Journal of Social Psychiatry 62 (3), 235-242. doi: 10.1177/0020764015623974.

Harvey, C.A., Jeffreys, S.E., McNaught, A.S., Blizard, R.A., King, M.B., 2007. The Camden Schizophrenia Surveys. III: Five-year outcome of a sample of individuals from a prevalence survey and the importance of social relationships. International Journal of Social Psychiatry 53 (4), 340-56.

Ibi, D., González-Maeso, J., 2015. Epigenetic signaling in schizophrenia. Cell Signal 27 (10), 2131-2136. doi: 10.1016/j.cellsig.2015.06.003.

IBM Corp., 2016. IBM SPSS Statistics for Windows, version 24.0. Armonk, NY: IBM Corp.

Järvelin, M.R., Hartikainen-Sorri, A.L., Rantakallio, P., 1993. Labour induction policy in hospitals of different levels of specialisation. British Journal of Obstetrics and Gynaecology 100, 310–315.

Kahn, R., Sommer, I., Murray, R., Meyer-Lindenberg, A., Weinberger, D., Cannon, T., et al., 2015. Schizophrenia. Nature Reviews Disease Primers, Nov 12 (1), 15067. doi:10.1038/nrdp.2015.67

Käkelä, J., Panula, J., Oinas, E., Hirvonen, N., Jääskeläinen, E., Miettunen, J., 2014. Family history of psychosis and social, occupational and global outcome in schizophrenia: A meta-analysis. Acta Psychiatrica Scandinavica 130 (4), 269-278.

Käkelä, J., Marttila, R., Keskinen, E., Veijola, J., Isohanni, M., Koivumaa-Honkanen, H., et al., 2017. Association between family history of psychiatric disorders and long-term outcome in schizophrenia - The Northern Finland Birth Cohort 1966 study. Psychiatry Research 249, 16-22. doi: 10.1016/j.psychres.2016.12.040. Epub 2016 Dec 27.

Kilian, S., Asmal, L., Chiliza, B., Olivier, M.R., Phahladira, L., Scheffler, F., et al., 2017. Childhood adversity and cognitive function in schizophrenia spectrum disorders and healthy controls: evidence for an association between neglect and social cognition. Psychol Med. Dec 22, 1-8. doi: 10.1017/S0033291717003671. [Epub ahead of print]

Macbeth, A., Gumley, A., Harder, S., O´Flaherty, S., 2015. Risk of psychotic disorder in offspring of parents with schizophrenia: a meta-analysis. European Archives of Psychiatry and Clinical Neuroscience 265, Supplement O-01-002.

Matevosyan, N.R., 2011. Pregnancy and postpartum specifics in women with schizophrenia: a meta-study. Archives if Gynecology and Obstetrics 283 (2), 141–147.

McGlashan, T.H., 1986. The prediction of outcome in chronic schizophrenia. IV. The Chestnut Lodge follow-up study. Archives of General Psychiatry 43, 167-176.

Meier, S.M., Agerbo, E., Maier, R., Pedersen, C.B., Lang, M., Grove, J., et al., 2016. High loading of polygenic risk in cases with chronic schizophrenia. Molecular Psychiatry 21 (7), 969-974. doi: 10.1038/mp.2015.130.

Mortensen, P.B., Pedersen, M.G., Pedersen, C.B., 2010. Psychiatric family history and schizophrenia risk in Denmark: Which mental disorders are relevant? Psychological Medicine, 40 (2), 201-210.

Okasha, T., Zaki, N., Meguid, M.A., El-Missiry, M., Sabry, W., Ismaeil, M.K., et al., 2016. Duration of untreated psychosis in an Egyptian sample: Sociodemographic and clinical variables. International Journal of Social Psychiatry Sep 28. pii: 0020764016670429. [Epub ahead of print].

Pruessner, M., King, S., Vracotas, N., Abadi, S., Iyer, S., Malla, A.K., et al., 2018. Gender differences in childhood trauma in first episode psychosis: Association with symptom severity over two years. Schizophr Res. Jun 21. pii: S0920-9964(18)30381-5. doi: 10.1016/j.schres.2018.06.043. [Epub ahead of print]

Rasic, D., Hajek, T., Alda, M., Uher, R., 2014. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: A meta-analysis of family high-risk studies. Schizophrenia Bulletin 40 (1), 28-38.

Shorter, K.R., Miller, B.H., 2015. Epigenetic mechanisms in schizophrenia. Progress in Biophysics and Molecular Biology 118 (1-2), 1-7. doi: 10.1016/j.pbiomolbio.2015.04.008.

Singh, T., Kurki, M., Curtis, D., Purcell, S.M., Crooks, L., McRae, J., et al., 2016. Rare loss-of-function variants in SETD1A are associated with schizophrenia and developmental disorders. Nature Neuroscience 19 (4), 571-577. doi: 10.1038/nn.4267.

Smeets, F., Lataster, T., Viechtbauer, W., Delespaul, P., Bruggeman, R., Cahn, W., et al., 2015. Evidence that environmental and genetic risks for psychotic disorder may operate by impacting on connections between core symptoms of perceptual alteration and delusional ideation. Schizophrenia Bulletin 41 (3), 687-697.

Suvisaari, J.M., Haukka, J., Tanskanen, A., Lönnqvist, J.K., 1998. Age at onset and outcome in schizophrenia are related to the degree of familial loading. British Journal of Psychiatry 173, 494-500.

Suvisaari, J., Perälä, J., Viertiö, S., Saarni, S.I., Tuulio-Henriksson, A., Partti, K., et al., 2012. Psykoosien esiintyvyys ja alueellinen vaihtelu Suomessa. Suom. Lääk. 67, 677-83.

Walder, D.J., Faraone, S.V., Glatt, S.J., Tsuang, M.T., Seidman, L.T., 2014. Genetic liability, prenatal health, stress and family environment: risk factors in the Harvard Adolescent Family High Risk for schizophrenia study. Schizophrenia Research 157 (1–3), 142–148.

Wan, M.W., Salmon, M.P., Riordan, D.M., Appleby, L., Webb, R., Abel, K.M., 2007. What predicts poor mother-infant interaction in schizophrenia. Psychological Medicine 37 (4), 537–546.

Xiao, L., Shen, T., Peng, D.H., Shu, C., Jiang, K.D., Wang, G.H., 2013. Functional -141C Ins/Del polymorphism in the dopamine D2 receptor gene promoter and schizophrenia in a Chinese Han population. J. Int. Med. Res. 41 (4), 1171-8. doi: 10.1177/0300060513483415. Epub 2013 Jul 1.

Table 1. Parental mental disorders by background variables of study subjects.

	Parental psychosis			Any parental psychiatric disorder		
	No	Yes	p-value	No	Yes	p-value
	n (%)	n (%)		n (%)	n (%)	
Gender			0.534			0.776
Male	89 (88.1)	12 (11.9)		53 (52.5)	48 (47.5)	
Female	80 (90.9)	8 (9.1)		48 (54.5)	40 (45.5)	
Psychosis diagnosis			0.781			0.369
Schizophrenia	41 (93.2)	3 (6.8)		25 (56.8)	19 (43.2)	
Schizoaffective/ delusional disorder	13 (86.7)	2 (13.3)		9 (60.0)	6 (40.0)	
Other psychosis	115 (88.5)	15 (11.5)		67 (51.5)	63 (48.5)	
	mean (sd)	mean (sd)		mean (sd)	mean (sd)	
Age of illness onset	21.2 (4.0)	21.3 (4.2)	0.925	21.7 (3.9)	20.7 (4.1)	0.071
Length of follow-up	8.8 (4.0)	8.8 (4.2)	0.951	8.3 (3.9)	9.4 (4.1)	0.082

Table 2. Association between psychosis diagnosis and outcome in psychotic disorders.

	Psychosis diagnosis		
	Schizophrenia spectrum[1] (n=59)	Other psychosis[2] (n=130)	
	Median (IQR)[3]	Median (IQR)	p-value[4]
Hospital treatment			

Days at hospital	157 (61-335)	17 (1-97)	<0.001
Number of hospitalisations	4.0 (2.0-8.0)	2.0 (0.8-4.0)	<0.001
Proportion of time spent at hospital	5.0% (2.4-10.4%)	0.7% (0.0-3.1%)	<0.001
	n (%)	n (%)	p-value[5]
Disability pension			0.021
No	42 (71)	111 (85)	
Yes	17 (29)	19 (15)	
Cumulative number of work days in 2014-2015			0.001
≤25% of work days	47 (80)	71 (55)	
>25% of work days	12 (20)	59 (45)	

[1]Schizophrenia spectrum: schizophrenia, schizophreniform, schizoaffective or delusional disorder, [2]Other psychosis: other non-organic psychosis than schizophrenia spectrum, [3]IQR = interquartile range, [4]Statistical significance based on Mann-Whitney U test, [5]Statistical significance based on chi square test.

Table 3. Association between parental psychosis and outcome in psychotic disorders.

	Parental psychosis		
	No (n=169)	Yes (n=20)	
	Median (IQR)[1]	Median (IQR)	p-value[2]
Hospital treatment			
Days at hospital	43 (2-169)	45 (2-185)	0.852
Number of hospitalisations	2.0 (1.0-5.0)	2.0 (1.0-3.8)	0.500
Proportion of time spent at hospital	1.6% (0.0-5.9%)	1.7% (0.2-4.5%)	0.914
	n (%)	n (%)	p-value[3]
Disability pension			0.909
No	137 (81)	16 (80)	
Yes	32 (19)	4 (20)	
Cumulative number of work days in 2014-2015			0.460
≤25% of work days	104 (62)	14 (70)	
>25% of work days	65 (38)	6 (30)	

[1]IQR = interquartile range, [2]Statistical significance based on Mann-Whitney U test, [3]Statistical significance based on chi square test.

Table 4. Association between any parental psychiatric disorder and outcome in psychotic disorders.

	Any parental psychiatric disorder		
	No (n=101)	Yes (n=88)	
	Median (IQR)[1]	Median (IQR)	p-value[2]
Hospital treatment			
Days at hospital	26 (0-147)	68 (6-215)	**0.035**

Number of hospitalisations	2.0 (0.0-4.5)	2.0 (1.0-7.0)	**0.039**
Proportion of time spent at hospital	0.8% (0.0-5.6%)	2.3% (0.2-5.9%)	0.085
	n (%)	n (%)	p-value[3]
Disability pension			0.229
No	85 (84)	68 (77)	
Yes	16 (16)	20 (23)	
Cumulative number of work days in 2014-2015			0.128
≤25% of work days	58 (57)	60 (68)	
>25% of work days	43 (43)	28 (32)	

[1]IQR = interquartile range, [2]Statistical significance based on Mann-Whitney U test, [3]Statistical significance based on chi square test. Statistically significant p-values in **bold**.