Family history of psychiatric disorders and age at first contact in schizophrenia: an epidemiological study*

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Background The risk for schizophrenia has been associated with a family history of this and other psychiatric disorders. The relationship between age at first contact and family history of psychiatric illness is not certain.

Aims To estimate the risks for schizophrenia associated with a range of psychiatric diagnoses in family members and to investigate the relationship between these risks and age at first contact for schizophrenia.

Method A nested case–control study design was employed. Psychiatric admission data and socio-economic data were available for 7704 cases admitted between 1981 and 1998 in Denmark, 192 590 gender- and age-matched controls, and for the parents and siblings of all subjects.

Results Controlling for socio-economic factors, risk for schizophrenia was associated with a family history of all psychiatric disorders except substance misuse and independently with a family history of suicide. The risk for schizophrenia associated with a family history of psychiatric disorders decreased as age at first contact increased.

Conclusions Risk for schizophrenia is associated with a range of psychiatric disorders in family members and these risks are not constant across the risk period.

Declaration of interest None.

*Presented in part at the European First Episode Schizophrenia Network Meeting, Whistler BC, Canada, 27 April 2001.

Family studies have confirmed the familial nature of schizophrenia (Gottesman, 1991). However, the relationship (if any) between risk for schizophrenia and the presence of other psychiatric disorders in the family is less clear. Whether age at onset of schizophrenia is related to a family history of the disorder has been investigated (Kendler *et al*, 1987, 1996; Shimizu *et al*, 1988; Kendler & MacLean, 1990; Pulver & Liang, 1991; Sham *et al*, 1994; Suvisaari *et al*, 1998), and although the findings have not been consistent there is some evidence that those with higher familial loading for schizophrenia also have an earlier age at onset of the disorder (Kendler & MacLean, 1990; Pulver *et al*, 1990; Suvisaari *et al*, 1998). We estimated the risk for schizophrenia associated with a range of psychiatric disorders in parents and siblings of cases with schizophrenia compared with matched controls, and investigated the interactions between family psychiatric history and age at first contact for schizophrenia.

METHOD

The data were based on Danish longitudinal registers that were merged using a unique personal identification number known as the CPR number. The CPR number is the equivalent of a person's social security number and is used across all registration systems in Denmark. All live-born children and new residents in Denmark are assigned a unique personal identification number and information is kept under this number in all national registers, thus ensuring accurate linkage of information between registers without the necessity to reveal a person's identity. The CPR registry was instigated in 1968 (Malig, 1996).

The socio-economic data were obtained from the Integrated Database for Longitudinal Labour Market Research or IDA database (Danmarks Statistiks, 1991), which includes linked information on employees and establishments. Data for this register comes from a number of administrative registers, e.g. the Danish tax authorities, the employment register, the CPR register and the education register, and can be followed over time. The information on people relates to the status in the last week of November in each year and there is continuous annual information available from 1980 to 1998. The register covers the total population and includes information on employment, education, marital status and income. All jobs are included and for each, information is available regarding the percentage of time during the year in work, salary, social benefits received during the year and type of job. For our purposes a random 5% sample of this register in addition to the patients and their families was used as the sample base from which the controls and their families were taken.

The Danish Psychiatric Central Register has monitored all psychiatric in-patient facilities in Denmark since 1969 (Munk-Jorgensen & Mortensen, 1997). There are no private psychiatric facilities in Denmark and all treatment is free of charge. All diagnoses were according to the WHO International Classification of Diseases, eighth revision (ICD–8; World Health Organization, 1967) until the end of December 1993 and according to the ICD–10 (World Health Organization, 1992) from January 1994. Parental and sibling psychiatric information related to the status before the date of first contact of the case so that only family members who had had a psychiatric contact before or on this date contributed information to the calculation of the risk associated with family history.

Study design

A time-matched, nested case–control study design (Clayton & Hills, 1993) was used to select the control sample.

Study population

For each case, 25 controls were randomly selected from a subsample of all available controls fulfilling the matching criteria, i.e. were born in the same calendar year, were of the same gender, and had not been admitted to a psychiatric facility in Denmark before the date that the case was first admitted.

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Cases

The study sample comprised all persons aged over 15 years admitted to a Danish psychiatric facility for the first time between 1981 and 1998 with an ICD–8 295 or ICD–10 F20 diagnosis of schizophrenia and known maternal identity. A total of 7704 persons with schizophrenia were identified, 92% had links to a father (paternity not known/declared in 8%) and 66% were male.

Controls

The control sample consisted of 192 590 individuals, representing 25 controls per case, individually matched to the case on date of first admission and gender and identified in the IDA database. The controls had the same gender and age distribution as the cases and 96% had links to a father.

Socio-economic and demographic variables

Socio-economic and demographic data were included in this study to control for the possible effects of confounding. Information included in the study was extracted from the IDA database for cases, controls and their parents and siblings for the year before the date when the person was first admitted. We included information on occupational status in the following categories: self-employed; paid employment; student; not in the work force; and labour market status missing. For parents, we included educational level according to three categories including basic education, high school education and vocational training, and university level. We included a more detailed description of education for the cases, including: basic school; high school; vocational training; high school +3 years; bachelor's degree; and Master's degree, doctorate. Other demographic variables included were marital status, defined as single or married (including cohabiting), being the parent of a child and parental age at birth of subject (grouped as <20, 20–25, 26–30, 31–35, 36–40, >40 years).

Family history

It was possible to obtain information relating to family history of psychiatric contacts for mothers, fathers and siblings by linking with the Danish Psychiatric Central Register. Initially the history of psychiatric disorders in family members was defined in a hierarchical manner as follows: schizoaffective disorder; schizophrenia; schizophrenia-like psychosis; bipolar disorder; other affective disorder; other psychiatric disorder; and in addition to the hierarchy, a history of substance misuse and suicide. To increase statistical power and to simplify the models involving the interaction between family history and age at first contact, controlling for socio-economic and demographic variables, history of psychiatric disorders in family members was combined into groups as follows: (a) schizophrenia, schizoaffective disorder, and schizophrenia-like psychosis (ICD–8: 295, 295.7, 297, 298.39, 301.83; and ICD–10: F20, F25, F21–F24, F28, F29); (b) bipolar illness and other affective illness (ICD–8: 296.1, 296.3, 296, 300.4; and ICD–10: F30, F31, F34.0, F32–F39); (c) other psychiatric disorder (any other diagnosis). Additional categories included family history of substance misuse disorders (ICD–8: 303, 304; and ICD–10: F10.2, F11.2, F12.2, F13.2, F14.2, F15.2, F16.2, F17.2, F18.2, F19.2) and a history of suicide in mothers, fathers and siblings as identified in the Cause of Death Register (Sundhedsstyrelsen, 1992).

Statistical analysis

The data were analysed in a conditional logistic regression model using the PhReg procedure in SAS version 6.12 for Windows NT (SAS Institute, 1997) and asymptotic 95% confidence intervals were calculated. Variables were assessed the last full year before the first admission ever to a psychiatric hospital, irrespective of whether schizophrenia was diagnosed at first admission or later. The method of sampling controls, risk-set sampling with the replacement of controls after selection, means that the odds ratio estimate in the analyses can be interpreted as an incidence rate ratio (IRR) between exposed and unexposed categories (Flanders & Louv, 1986).

RESULTS

In Table 1 the sample is described according to gender, marital status, being a parent, educational level, employment status, family history of psychiatric disorders (mothers, fathers and siblings), age at first contact, maternal and paternal age at birth and whether there was a reference to a father.

The results of the initial univariate models examining the risks for schizophrenia associated with having a paternal, maternal or sibling history of psychiatric disorders is given in Table 2. In Table 3 we present the IRR for family history groups according to the combined categorisation. The results of the univariate models are displayed, along with the results of the model adjusting for socio-economic and demographic factors and the interaction between family history of psychiatric illness and age at first contact.

Gender differences in risk according to parental psychiatric history

There was no significant difference ($t=-1.08$, d.f. 7702, $P=0.27$) between age at first contact for males (mean=25.27 years, s.d. 5.94) and females (mean=25.12 years, s.d. 6.02) in this sample. Based on the combined family history categorisation, we found no significant gender differences in risk for schizophrenia within family history categories; females and males had similar risks within maternal and paternal family history categories. There was a significantly higher risk associated with a maternal psychiatric history of schizophrenia and affective disorder (Wald $\chi^2=4.47$ and 4.33, respectively; $P<0.03$), but not other psychiatric disorders (Wald $\chi^2=0.002$; $P<0.99$) compared with the respective paternal diagnoses.

Interaction between family psychiatric history and age at first contact for schizophrenia

The significance of the interaction between family psychiatric history and age at first contact was tested to examine whether the risk for schizophrenia associated with a family psychiatric history was similar across all ages of first contact. We found significant interactions between age at first contact and maternal history of schizophrenia (IRR 0.96; 95% CI 0.94–0.99; $P<0.001$), affective disorders (IRR 0.97; 95% CI 0.95–0.99; $P<0.02$) and other psychiatric disorders (IRR 0.98; 95% CI 0.96–0.99; $P<0.02$), for paternal history of other psychiatric disorders (IRR 0.98; 95% CI 0.96–0.99; $P<0.02$), and for all categories of psychiatric disorders for all relatives combined: schizophrenia (IRR 0.98; 95% CI 0.96–0.99; $P<0.002$), affective disorders (IRR 0.98; 95% CI 0.96–0.99; $P<0.01$) and other psychiatric disorders (IRR 0.98; 95% CI 0.96–0.99; $P<0.001$). The IRRs associated with the significant interaction terms were less than 1, indicating that the

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risk associated with a family history increases as age at first contact decreases.

The interactions remained significant after controlling for the interaction between parental psychiatric history (maternal schizophrenia, paternal schizophrenia, maternal affective disorder, paternal affective disorder, maternal other diagnosis, paternal other diagnosis) and calendar year of admission, and the interaction between parental psychiatric history, calendar year of admission and age at first contact. We tested for these interactions to investigate whether the relationship between history of familial psychiatric disorders and age at first contact could be explained by the possibility that better information regarding family psychiatric history was available for the younger cases compared with the older cases. These interactions were not significant, suggesting that the quality of psychiatric history data was not the source of the significant interactions between age at first contact and parental psychiatric history. We did not find significant interactions between age at first contact and sibling psychiatric history or paternal history of schizophrenia or affective disorder.

We calculated the risks associated with a family history of psychiatric disorders for different ages of first contact for the categories of family history where a significant interaction was found (as reported above). The estimated risks and the 95% confidence intervals are presented in Table 4 and were calculated according to the method described by Hosmer & Lemeshow (1989).

It is clear that the greatest risks were observed in the younger cases with a maternal history of a schizophrenic disorder and the risk declined as the age at first contact increased. This was also the case for offspring of mothers with affective disorders and for offspring of mothers and fathers with other psychiatric disorders. We included a second-order term (the age at first contact multiplied by family history squared) in the model to test the validity of the interaction term. This was not significant, indicating the validity of the original model including the linear interaction term to explain the relationship between age at first contact and family history for psychiatric disorders.

In order to more closely examine the interaction between age at first contact and family history we further divided age at first contact into a number of arbitrarily

Table 1 Sample characteristics defined in the year prior to case first contact

	Cases, *n* (%), *n*=7704	Controls, *n* (%), *n*=192 590
Males	5170 (67)	
Marital status		
Single	912 (11.84)	73 322 (38.07)
Married/cohabiting	6792 (88.16)	119 268 (61.93)
Being a parent		
At least one child	1389 (18.03)	98 899 (51.35)
No children	6315 (81.97)	93 691 (48.65)
Education		
No information	297 (3.86)	3415 (1.77)
Basic school	4485 (58.22)	87 055 (45.20)
High school	1040 (13.50)	21 957 (11.40)
Vocational training	1369 (17.77)	59 720 (31.01)
Shorter: high school +3 years	157 (2.04)	6397 (3.32)
Medium: Bachelor's, high school +3–4 years	175 (2.27)	8491 (4.41)
Masters'/doctorate	181 (2.35)	5555 (2.88)
Employment		
Self-employed	58 (0.75)	4322 (2.24)
White-collar worker	497 (6.45)	42 297 (21.96)
Blue-collar worker	1232 (15.99)	66 872 (34.72)
Disability pensioner	226 (2.29)	1139 (0.59)
Student	975 (12.66)	19 310 (10.03)
Outside workforce	1058 (13.73)	6410 (3.33)
Less than 100% of year in work	3658 (47.48)	52 240 (27.12)
Maternal history of psychiatric disorders		
Schizoaffective disorder	46 (0.60)	92 (0.05)
Schizophrenia	151 (1.96)	491 (0.25)
Schizophrenia-like psychosis	190 (2.47)	974 (0.51)
Bipolar affective disorder	45 (0.58)	459 (0.24)
Other affective disorders	227 (2.95)	2764 (1.44)
Other psychiatric disorders	572 (7.42)	6566 (3.41)
No psychiatric history	6473 (84.02)	181 244 (94.11)
Substance misuse[1]	333 (4.32)	2952 (1.53)
Paternal history of psychiatric disorders		
Schizoaffective disorder	10 (0.13)	32 (0.02)
Schizophrenia	61 (0.79)	277 (0.14)
Schizophrenia-like psychosis	76 (0.99)	526 (0.27)
Bipolar affective disorder	39 (0.51)	360 (0.19)
Other affective disorders	101 (1.31)	1561 (0.81)
Other psychiatric disorders	497 (6.45)	5957 (3.09)
No known psychiatric history	6920 (89.82)	183 877 (95.48)
Substance misuse[1]	366 (4.75)	3994 (2.07)
Sibling history of psychiatric disorders		
Schizoaffective disorder	26 (0.19)	81 (0.03)
Schizophrenia	255 (1.88)	868 (0.27)
Schizophrenia-like psychosis	58 (0.43)	280 (0.09)
Bipolar affective disorder	14 (0.10)	131 (0.04)
Other affective disorders	38 (0.28)	379 (0.16)
Other psychiatric disorders	367 (2.71)	4032 (1.24)
No psychiatric history	12 802 (94.41)	317 942 (98.22)
Substance misuse[1]	227 (2.95)	1611 (0.50)

(continued)

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Table 1 *(continued)*

	Cases, *n* (%), *n*=7704	Controls, *n* (%), *n*=192 590
Age at first contact, years		
<20	1571 (20.4)	
20–24	2640 (34.3)	
25–29	1901 (24.7)	
30–34	1012 (13.1)	
35–39	428 (5.5)	
⩾40	152 (2.0)	
Maternal age at birth	26.88 (5.78)	26.67 (5.48)
Paternal age at birth	30.44 (7.02)	30.07 (6.53)
Paternal reference not available	607 (7.88)	7425 (3.86)

1. Substance misuse was not included in the diagnostic hierarchy and is reported independently.

chosen categories (<17, 18–20, 21–23, 24–26, 27–29, 30–33, 34–37, ⩾38 years) and assessed the interaction in each category (where a significant age interaction had been found in the previous model). The results of this analysis are shown in Table 5.

For maternal history of affective disorders and maternal and paternal history of other psychiatric disorder, the oldest group was defined as ⩾34, as the numbers did not permit us to split the ages further. For maternal history of affective disorder the youngest category was defined as <20, as the numbers in this category did not permit us to break the ages down further. The findings were very similar in the two approaches, which were statistically indistinguishable. Inevitably a degree of measurement error was introduced by examining the interactions in categories of age at first contact (Altman, 1991), although the results appear similar to those derived from the model with a single interaction term. The advantage of the single interaction term is that only one parameter is needed to express the interaction, whereas with age categories many more parameters are introduced into the model; also, although the categories were chosen to represent small bands of age, they were essentially arbitrary.

DISCUSSION

Family history of psychiatric disorders and risk for schizophrenia

The risk for schizophrenia was increased in those with a family history of all psychiatric disorders (except substance misuse) and with a family history of suicide (particularly for fathers). This finding supports the view that schizophrenia could be genetically related to other psychiatric disorders, particularly affective disorders (Maier *et al*, 1999) including major depression and with 'other' psychiatric disorders leading to psychiatric admission. We found that a history of suicide in the family was independently associated with an increased risk for schizophrenia. The IRR associated with a family history of suicide was similar to that for a family history of affective disorders, possibly reflecting undiagnosed affective disorders in this group.

It is possible that for some cases, schizophrenic disorders existed in the wider family circle, e.g. in grandparents or uncles and aunts. If this were so, then it could be that we have overestimated the effect of disorders other than schizophrenia in our sample. It is unlikely that this could account entirely for the increased risks associated with a family history of disorders other than schizophrenia; however, we were not able to test this.

Our risk estimates are similar to previous Danish estimates (Mortensen *et al*, 1999; Pedersen & Mortensen, 2001); however, for the first time we have been able to control for the possible confounding effects of socio-economic factors. Controlling for personal and familial socio-economic factors, the risk for schizophrenia associated with a family history of psychiatric disorders was somewhat reduced but remained high and significant.

Gender effects

We did not find any difference between the ages at first contact for males and females. However, the lack of gender differences in age at onset has been previously reported (Jablensky & Cole, 1997; Suvisaari *et al*, 1998). This can in

Table 2 Risk (incidence rate ratio, IRR) for schizophrenia associated with family history of psychiatric illness; univariate analyses

	Paternal psychiatric history IRR (95% CI)	Maternal psychiatric history IRR (95% CI)	Sibling psychiatric history IRR (95% CI)	All affected relatives IRR (95% CI)
Schizoaffective disorder	8.58 (4.21–17.51)	13.77 (9.63–19.71)	8.58 (5.51–13.38)	8.98 (6.85–11.75)
Schizophrenia	5.76 (4.33–7.67)	8.41 (6.97–10.14)	7.79 (6.68–9.10)	6.51 (5.81–7.30)
Schizophrenia-like psychosis	3.77 (2.94–4.84)	5.32 (4.53–6.24)	5.50 (4.13–7.34)	4.28 (3.76–4.86)
Bipolar illness	2.90 (2.08–4.06)	2.67 (1.97–3.64)	2.82 (1.62–4.91)	2.47 (1.99–3.07)
Other affective illness	1.73 (1.40–2.13)	2.23 (1.94–2.57)	2.70 (1.93–3.78)	1.85 (1.65–2.08)
Other psychiatric disorder	2.21 (1.94–2.50)	2.37 (2.14–2.61)	2.43 (2.15–2.74)	2.10 (1.95–2.26)
Substance misuse	1.07 (0.92–1.24)	1.09 (0.95–1.25)	1.05 (0.88–1.24)	1.08 (0.99–1.19)
Suicide	1.48 (1.21–1.81)	1.28 (0.98–1.69)	1.23 (0.83–1.81)	1.36 (1.16–1.59)
No reference to father	2.31 (2.11–2.52)			2.03 (1.86–2.22)
Unaffected (reference)	1.00	1.00	1.00	1.00

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Table 3 Risks (incidence rate ratio, IRR) for schizophrenia according to the combined family history categories

	Univariate model IRR (95% CI)	Adjusted model[1] IRR (95% CI)
Paternal history		
Schizophrenia	4.61 (3.83–5.56)	3.70 (2.97–4.61)
Affective illness	1.94 (1.63–2.33)	1.46 (1.20–1.78)
Other psychiatric disorder	2.20 (1.94–2.50)	1.73 (1.50–1.99)
No reference to father	2.31 (2.12–2.52)	1.27 (1.03–1.56)
Substance misuse	1.07 (0.92–1.24)	0.94 (0.80–1.11)
Suicide	1.47 (1.20–1.80)	1.38 (1.10–1.74)
Not affected (reference)	1.00	1.00
Maternal history		
Schizophrenia	6.78 (6.02–7.63)	4.86 (4.23–5.59)
Affective illness	2.29 (2.01–2.61)	1.91 (1.65–2.20)
Other psychiatric disorder	2.36 (2.14–2.61)	1.74 (1.56–1.95)
Substance misuse	1.09 (0.96–1.25)	0.91 (0.78–1.06)
Suicide	1.28 (0.97–1.68)	1.19 (0.87–1.63)
Not affected (reference)	1.00	1.00
Sibling history		
Schizophrenia	7.31 (6.38–8.37)	4.88 (4.16–5.73)
Affective illness	2.73 (2.04–3.64)	2.51 (1.80–3.51)
Other psychiatric disorder	2.42 (2.15–2.73)	1.80 (1.57–2.06)
Substance misuse	1.05 (0.89–1.24)	0.94 (0.78–1.15)
Suicide	1.25 (0.85–1.84)	1.38 (0.90–2.13)
Not affected (reference)	1.00	1.00
All affected relatives		
Schizophrenia	5.94 (5.45–6.46)	5.04 (4.58–5.55)
Affective illness	1.95 (1.76–2.17)	1.80 (1.61–2.02)
Other psychiatric disorder	2.09 (1.94–2.25)	1.85 (1.70–2.02)
No reference to father	2.04 (1.86–2.22)	1.27 (1.03–1.56)
Substance misuse	1.09 (0.99–1.95)	0.98 (0.88–1.08)
Suicide	1.36 (1.16–1.58)	1.30 (1.09–1.55)
Not affected (reference)	1.00	1.00

1. Model adjusted for family education, employment, reference to a father, history of suicide, psychiatric history; case: marital status, education, employment, being a parent to a child, parental age at birth, place of birth (Denmark or other country) and interaction between age at first contact and family history of psychiatric disorders.

part be attributed to the fact that the sample was essentially young with a relative absence of late-onset cases. The inclusion criteria required that for each person there was a link to a mother and links to mothers are most complete for those born since 1960. The relative absence of late-onset cases could also be part of the reason why there are fewer females than males in the sample (33% *v.* 66%); however, it is not uncommon to find fewer females than males in a sample based on treated incidence (Munk-Jorgensen, 1986; Jablensky & Eaton, 1995).

We found a higher risk associated with family history of maternal psychiatric illness compared with paternal illness and the lack of gender differences within these categories. It has previously been described that relatives of females with schizophrenia have a higher risk for schizophrenia than the relatives of males (Goldstein *et al*, 1990). Also males typically develop illness at a younger age than females, reducing the likelihood that they will produce offspring. Fertility rates are reduced in schizophrenia (McGrath *et al*, 1999). In this sample there was an increased risk in those without a reference to a father. It is unlikely that this increased risk is the result of an overrepresentation of psychopathology in these fathers (Mortensen *et al*, 1999) and perhaps indicates a social explanation. Additionally, paternity is known to be less certain than maternity, leading to non-differential misclassification of exposure in both cases and controls, the most likely effect of which would be to bias the estimates toward null values.

Table 4 Incidence rate ratio (IRR) and 95% CI estimated for selected ages to illustrate the significant age at first contact by family history interactions: model with a single interacting term

Age categories	Mother: schizophrenia	Mother: affective disorder	Mother: other psychiatric disorders	Father: other psychiatric disorders	All relatives: schizophrenia	All relatives: affective disorder	All relatives: other psychiatric disorders
>16	6.87 (5.46–8.66)	2.42 (1.88–3.13)	2.14 (1.78–2.56)	2.18 (1.76–2.69)	6.28 (5.34–7.40)	2.22 (1.81–2.72)	2.33 (2.05–2.65)
19	6.14 (5.12–7.34)	2.23 (1.83–2.73)	1.99 (1.72–2.30)	2.02 (1.69–2.40)	5.85 (5.14–6.65)	2.07 (1.77–2.43)	2.15 (1.94–2.39)
22	5.47 (4.74–6.33)	2.06 (1.75–2.42)	1.86 (1.65–2.09)	1.87 (1.61–2.17)	5.44 (4.91–6.03)	1.93 (1.70–2.19)	1.99 (1.83–2.17)
25[1]	4.89 (4.25–5.62)	1.90 (1.64–2.19)	1.73 (1.55–1.93)	1.73 (1.50–1.99)	5.06 (4.60–5.57)	1.80 (1.61–2.02)	1.84 (1.70–1.99)
28	4.36 (3.70–5.15)	1.75 (1.49–2.06)	1.61 (1.42–1.83)	1.60 (1.37–1.87)	4.71 (4.23–5.26)	1.68 (1.49–1.90)	1.70 (1.55–1.86)
32	3.75 (2.98–4.72)	1.57 (1.26–1.95)	1.47 (1.24–1.74)	1.45 (1.18–1.77)	4.28 (3.69–4.97)	1.53 (1.30–1.81)	1.53 (1.35–1.72)
35	3.34 (2.50–4.47)	1.44 (1.09–1.90)	1.37 (1.10–1.69)	1.34 (1.05–1.71)	3.99 (3.30–4.81)	1.43 (1.16–1.77)	1.41 (1.22–1.34)
38	2.99 (2.10–4.25)	1.33 (0.95–1.87)	1.27 (0.98–1.65)	1.24 (0.93–1.66)	3.70 (2.95–4.66)	1.33 (1.03–1.73)	1.30 (1.09–1.56)

1. Age 25 is the reference category.
Confidence intervals not including unity denote statistical significance.
Model adjusted for family education, employment, reference to a father, history of suicide, psychiatric history; case: marital status, education, employment, being a parent to a child, parental age at birth, place of birth (Denmark or other country), and interaction between age at first contact and family history of psychiatric disorders.

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Table 5 Incidence rate ratio (IRR) and 95% CI estimated for categories of age chosen to model the interaction between age at first contact and family history of psychiatric disorders

Age categories	Mother: schizophrenia	Mother: affective disorder	Mother: other psychiatric disorders	Father: other psychiatric disorders	All relatives: schizophrenia	All relatives: affective disorder	All relatives: other psychiatric disorders
<17	8.50 (5.83–12.37)		2.56 (1.92–3.42)	2.03 (1.46–2.81)	7.50 (5.52–10.20)		2.45 (2.00–3.08)
18–20	5.44 (4.15–7.14)	2.25 (1.74–2.91)[2]	1.89 (1.53–2.34)	2.00 (1.59–2.51)	5.22 (4.20–6.47)	2.29 (1.84–2.85)[2]	2.11 (1.81–2.46)
21–24	4.37 (3.27–5.84)	2.24 (1.67–3.01)	1.44 (1.15–1.79)	1.46 (1.13–1.87)	5.46 (4.46–6.67)	1.83 (1.44–2.34)	1.58 (1.35–1.84)
25[1]	4.86 (4.23–5.59)	1.91 (1.65–2.02)	1.74 (1.56–1.95)	1.73 (1.50–1.99)	5.04 (4.58–5.55)	1.80 (1.61–2.02)	1.85 (1.70–2.00)
27–29	4.14 (2.99–5.74)	1.56 (1.12–2.16)	1.42 (1.11–1.83)	1.29 (0.97–1.71)	4.57 (3.64–5.74)	1.79 (1.39–2.28)	1.35 (1.13–1.60)
30–33	4.15 (2.67–6.44)	1.25 (0.79–1.99)	1.65 (1.22–2.23)	1.74 (1.24–2.44)	3.49 (2.55–4.78)	1.10 (0.76–1.59)	1.76 (1.42–2.18)
⩾34	3.03 (1.77–5.19)	1.07 (0.70–1.64)	1.38 (0.95–2.00)	1.27 (0.82–1.97)	3.12 (2.05–4.74)	1.37 (0.92–2.05)	1.31 (0.99–1.72)

1. Age 25 is the reference category.
2. Categories combined because of small numbers in one or other category.
Confidence intervals not including unity denote statistical significance.
Model adjusted for family education, employment, reference to a father, history of suicide, psychiatric history; case: marital status, education, employment, being a parent to a child, parental age at birth, place of birth (Denmark or other country), and interaction between age at first contact and family history of psychiatric disorders.

Age at first contact and family history

The risk associated with a family history of psychiatric disorders was not constant across all ages of first contact. The risk associated with a positive family history decreased as age at first contact increased. For example, according to our model the risk associated with a maternal history of schizophrenia decreases by 20% (95% CI 10–30%) over a 5-year period, or on average by 4% per year. The risk for schizophrenia associated with a family history of the disorder was highest for those younger than 17 years. The finding of a reduced age at onset with family history of psychiatric disorders is consistent with some earlier studies (Kendler & MacLean, 1990; Albus *et al*, 1994; Sham *et al*, 1994; Alda *et al*, 1996). We modelled age at first contact with the psychiatric services, not age at first schizophrenia diagnosis. It could be argued that children from families well-known to the psychiatric services might be more likely to be identified earlier than those from families without psychiatric contact. However, in a previous register-based study (Suvisaari *et al*, 1998), earlier age at first contact was not explained by a shorter interval between the occurrence of psychotic symptoms and first admission to hospital for those who already had an affected family member.

Implications

Our findings suggest aetiological heterogeneity within the sample with regard to risk from family history of psychiatric disorders. The simple distinction of family history positive versus family history negative could not accurately describe the risks for schizophrenia associated with a family history of psychiatric disorders for the sample. It is clear that these risks reduced as age at first contact increased. The risk associated with a family history of psychiatric disorders is clearly more critical in the early years of the risk period. Perhaps it will be important to incorporate age at first contact interactions in all studies investigating risk factors for schizophrenia. The findings have implications for the way that risk factors should be modelled. Modelling the 'average risk' might not give us a picture of the true distribution of the association between risk factors and outcome in samples.

The genetics of schizophrenia are complex and it is possible that the liability is shared with a number of other disorders. It might be that schizophrenia represents an extreme outcome, perhaps mediated by adverse environmental processes, which can be expressed by different, and milder, phenotypes. It is possible that environmental factors, for example obstetric complications, might interact with genetic predisposition to increase the risk for schizophrenia (Cannon *et al*, 1993).

Reduced age at first contact in those with a family history of psychiatric disorders might be the result of genetic factors or mediated by social and cultural factors (Jablensky & Cole, 1997), but we cannot be sure. If genetically mediated, it could have implications for modelling the transmission of schizophrenia, and/or for the calculation of the risks for illness in 'well' relatives of different ages. It perhaps has implications for genetic counselling.

ACKNOWLEDGEMENTS

This study was funded by the Stanley Foundation and the Danish National Research Foundation.

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CLINICAL IMPLICATIONS

- Risk for schizophrenia is increased in those with a family history of a range of psychiatric admissions and with a family history of suicide.
- Risk for schizophrenia associated with a family history of psychiatric disorders decreases as age at first contact increases.
- Controlling for case, and familial socio-economic factors, the risk for schizophrenia associated with family psychiatric history remains high.

LIMITATIONS

- The study included register-based clinical diagnoses.
- Family history information was limited to first-degree relatives.
- Late-onset cases were underrepresented in our sample.

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